ACT-539313

Binge Eating Disorder

Protocol ID-082A201

Multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of oral ACT-539313 in the treatment of adults with moderate to severe binge eating disorder

Study Phase:	2
EudraCT Number:	Not applicable
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SPONSOR CONTACT DETAILS

Sponsor	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
Medical Emergency Hotline Toll Telephone Number	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

COORDINATING INVESTIGATOR

Name / Title	**Address**
[redacted]	[redacted]

CONTRACT RESEARCH ORGANIZATION INFORMATION

Some study activities will be delegated to Contract Research Organizations (CROs). A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia

Treatment name / number

ACT-539313

Indication

Binge eating disorder

Protocol number, study title

ID-082A201

Multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of oral ACT-539313 in the treatment of adults with moderate to severe binge eating disorder.

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of ACT-539313, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	Name	Date	Signature
[redacted]	[redacted]	04.05.2021	[redacted]
[redacted]	[redacted]	04.05.2021	

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

ACT-539313

Indication

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Protocol number, study title

ID-082A201

Multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of oral ACT-539313 in the treatment of adults with moderate to severe binge eating disorder.

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on study participants (other than those procedures necessary for the well-being of the study participants).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws.

Principal Investigator	Country	Site number	Town	Date	Signature

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LIST OF ABBREVIATIONS AND ACRONYMS

AAT	Approach Avoidance Task
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APA	American Psychiatric Association
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration vs time curve
AUC_τ	Area under the plasma concentration vs time curve during a dose interval
b.i.d.	Twice daily
BE	Binge eating
BED	Binge eating disorder
BMI	Body mass index
BWSQ	Benzodiazepine Withdrawal Symptoms Questionnaire
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations (US)
CGI-C	Clinical Global Impression of Change scale
CGI-S	Clinical Global Impression of Severity scale
CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical study report
C-SSRS©	Columbia Suicide Severity Rating Scale©
CYP	Cytochrome P450
DB	Double-blind
DDI	Drug-drug interaction(s)

DSM-(IV/5)	Diagnostic and Statistical Manual of Mental Disorders (4^{th} / 5^{th} edition)
ECG	Electrocardiogram
eCRF	Electronic case report form
EDE-Q(7)	Eating Disorder Examination Questionnaire (7-item)
EOS	End-of-Study
EOT	End-of-Treatment
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FERT	Facial Expression Recognition Task
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GSET	Grip Strength Effort Task
HAMD-17	Hamilton Rating Scale for Depression (17-item)
HbA1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LSMean	Least squares mean
MAD	Multiple-ascending dose
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MINI©	Mini International Neuropsychiatric Interview©
MPS	Maier-Philipp subscale
[redacted]	[redacted]

OX1R	Orexin receptor type 1
OX2R	Orexin receptor type 2
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change scale
PGI-S	Patient Global Impression of Severity scale
PI	Principal investigator
PK	Pharmacokinetic(s)
POC	Proof-of-concept
PPS	Per-protocol analysis set
QTc	Corrected QT interval
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RND	All-randomized analysis set
RT	Reaction time
SAD	Single-ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCID-5	Structured Clinical Interview for DSM-5
SCR	Screened analysis set
SD	Standard deviation
SI	International system of units
SOC	System Organ Class
SSS	Stanford Sleepiness Scale
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
USPI	United States Prescribing Information
WHO	World Health Organization

WOCBP	Women of childbearing potential
YBOCS	Yale-Brown Obsessive-Compulsive Scale
YBOCS-BE	Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating

NON-SUBSTANTIAL AMENDMENT 2

Amendment rationale

This amendment applies to protocol ID-082A201 Version 2 dated 17 December 2020. The resulting amended global protocol is Version 3 dated 4 May 2021.

The purpose of this amendment is to simplify the language of, and therefore clarify, inclusion criterion #4 related to the definition of severity of BED assessed at screening (Visit 1).

As the definition of BED (inclusion criterion #3) is based on DSM-5, and since DSM-5 also includes a severity grading scale (while previous versions did not), it was considered appropriate to use that scale to define severity in inclusion criterion #4.

However, in this study the criterion for inclusion at randomization is based on binge eating days per week (criterion #9) rather than on binge eating episodes. An attempt was made to harmonize the definition of severity based on binge eating episodes, as per DSM-5, with the requirement of days with binge eating episodes (inclusion criterion #9) at randomization.

Inclusion criterion #4 reads: "*Self-reported BED severity of at least moderate level, defined in this study as 4–7 BE episodes per week, and spread out over ≥ 3 days, for a duration of ≥ 6 months*"

Feedback received from the study sites, however, showed that such a hybrid definition, consisting of both binge eating episodes and days, was too complex to interpret and may lead to confusion, and therefore requires revision.

With this protocol amendment, study inclusion criterion #4 now reads "*Self-reported BED severity of at least moderate level, defined as at least 4 BE episodes per week, on average, for a duration of at least 6 months*"

The rewording does not modify the target population, which remains identical to that described in previous protocol versions by inclusion criterion #9 (Section 5.3), assessed at Visit 2 (prior to randomization), which remains unchanged, and reads: *"Reporting ≥ 3 BE days for each of the 2 weeks prior to randomization as documented in the participant's BE diary and with BE diary entries completed for at least 6 days per week during this 2-week period (between Visit 1 and 2)."*

In addition, the following modifications have been made:

- In the Protocol Summary, correction of numbering for inclusion criterion 7, for consistency with core text in Section 5.3.

- Clarification on the administration of study drug on study visit days is provided in Section 6.1.6.3.
- Exclusion criterion #19 did not explicitly exclude morphine and other opioids, although these are listed in the relevant section on forbidden medications. Sections have been aligned for consistency.
- More detailed guidance on the recommended order of assessment/questionnaires is provided in Section 7.2.
- The SCID-5 version used in this protocol is a customized version of the standard one, and it should be referenced as Structured Clinical Interview for DSM-5 – Clinical Trial version. The title of Section 7.2.3.1 has been revised accordingly.
- Precision is added in Section 7.2.5.4 that all laboratory reports must be printed, reviewed, signed and dated by the investigator or delegate within 5 calendar days.
- Reiteration of the reference time frame for the eligibility assessment based on items 2, 3, 4 and 5 of the C-SSRS at Screening (exclusion criterion #26) is provided in Section 7.2.5.7 where the scale is discussed under "Safety assessments".
- Guidance has been added regarding COVID-19 vaccination during trial participation (Section 5.9.1.4).
- Instructions for completion of the Stanford Sleepiness Scale (Appendix 3) have been clarified.
- The C-SSRS version in Appendix 12 is slightly different from the version used in the electronic system. In section 'Intensity of ideation', Deterrents, the last item was not correct. Alignment with the ePRO version has been made.

Minor editorial corrections have also been made.

Changes to the protocol

Two versions of the amended protocol have been prepared: 1) a clean version and 2) a comparison document showing deletions and insertions in comparison to the previous protocol version.

Amended protocol sections

The main sections of the protocol affected by this global amendment are listed below.

Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis:

Section 5.1 Study participant population description

Section 5.3 Inclusion criteria

Section 5.4	Exclusion criteria
Section 5.9.1.4	COVID-19
Section 6.1.6.3	Study treatment dosing and administration
Section 7.2	Study assessments and procedures
Section 7.2.3.1	Structured Clinical Interview for DSM-5 – Clinical Trial Version (SCID-5)
Section 7.2.5.4	Clinical laboratory assessments
Section 7.2.5.7	Columbia Suicide Severity Rating Scale
Appendix 3	Stanford Sleepiness Scale
Appendix 12	Columbia Suicide Severity Rating Scale©

Summary of previous amendments

Amendment	Date	Main reason(s)
1	17 December 2020	• Implement the modifications requested by the FDA at the time of the IND review to ensure that the safety and well-being of the research participants are protected. • BED severity aligned with DSM-5 definition. • Remote assessments in the context of COVID-19 further described.

1 PROTOCOL SUMMARY

1.1 Synopsis

TITLE	Multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of oral ACT-539313 in the treatment of adults with moderate to severe binge eating disorder
OBJECTIVES	Evaluate the efficacy of ACT-539313 in the treatment of binge eating disorder (BED). Evaluate the safety and tolerability of ACT-539313 in participants with BED. Other objectives are described in Section 3.
ENDPOINTS	**Primary efficacy endpoint** The primary endpoint is the change from baseline to Week 12 in the number of binge eating (BE) days per week. A BE day is defined as a day with at least one confirmed BE episode. **Exploratory efficacy endpoints** • Change from baseline to Week 12 in the number of BE episodes per week. • Percentage of study participants without BE episodes during the last 4 weeks of the treatment period. • Change from baseline to Week 12 in the total score of the Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating (YBOCS-BE). • Change from baseline to Week 12 in the subscale scores (compulsive/obsessive, restraint, control) of the YBOCS-BE. • Change from baseline to Week 6 and to Week 12 in the Hamilton Rating Scale for Depression (17-item) (HAMD-17) total score. • Change from baseline to Week 6 and to Week 12 in the HAMD-17 subitems 10 and 11. • Change from baseline to Week 6 and to Week 12 in the HAMD-17 Maier-Philipp subscale (MPS) score. • Change from baseline to Week 12 in the Eating Disorder Examination Questionnaire (7-item; EDE-Q7) global score

	and 3 subscales scores (dietary restraint, shape/weight overvaluation, and body dissatisfaction). **Safety endpoints** • Treatment-emergent adverse events (TEAEs) defined as an adverse event (AE) occurring from the start of study treatment administration up to the End-of-Study (EOS). • Treatment-emergent serious AEs (SAEs) defined as an SAE occurring from the start of study treatment administration up to the EOS. • TEAEs leading to premature discontinuation of the study treatment. • Treatment-emergent AEs of special interest (AESIs), i.e., somnolence, from the start of study treatment administration up to the EOS. • Occurrence of daytime sleepiness assessed by Stanford Sleepiness Scale (SSS) from the start of study treatment administration up to Visit 4 (Week 2). • Treatment-emergent marked laboratory abnormalities from the start of study treatment administration to all assessed time points during the study. • Change in vital signs from baseline to all assessed time points during the study. • Medically relevant ECG abnormalities while on study treatment from baseline to all assessed time points during the study. • Occurrence of withdrawal symptoms upon treatment discontinuation, as measured by change between Week 12 / End-of-Treatment (EOT) and EOS visit, assessed by the Benzodiazepine Withdrawal Symptoms Questionnaire (BWSQ), and HAMD-17 total score. • Occurrence of suicidal ideation and/or behavior while on study treatment based on the Columbia Suicide Severity Rating Scale© (C-SSRS©) from baseline to all assessed time points during the study up to EOS. Details of endpoints are further described in Section 3.

DESIGN	ID-082A201 is a Phase 2, proof-of-concept, randomized, double-blind, parallel-group, multicenter study evaluating the efficacy and safety of 100 mg twice daily (b.i.d.) ACT-539313 in adults with moderate to severe BED versus placebo over a 12-week treatment period.
PERIODS	The study comprises the following consecutive periods: screening period (14–28 days), followed by a treatment period (12 weeks) and a safety follow-up period (7–13 days).
PLANNED DURATION	Approximately 14 months from first study participant, first visit to last study participant, last visit.
SITE(S)/ COUNTRY(IES)	Approximately 30 sites in the United States of America.
STUDY PARTICIPANTS / GROUPS	Approximately 120 study participants will be randomized to receive either ACT-539313 at a dose of 100 mg b.i.d. or placebo in a 1:1 ratio.
INCLUSION CRITERIA	Study participants must meet all the following inclusion criteria: **Criteria assessed at Visit 1:** 1. Signed and dated informed consent form prior to any study-mandated procedure. 2. Male or female study participants aged 18 to 55 years at the time of signing the informed consent form. 3. BED in accordance with Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria diagnosed using the Structured Clinical Interview for DSM-5 (SCID-5). 4. Self-reported BED severity of at least moderate level, defined as at least 4 BE episodes per week, on average, for a duration of at least 6 months. 5. BED in accordance with Eating Disorder Examination Questionnaire (EDE-Q). 6. Clinical Global Impression of Severity scale (CGI-S) score of ≥ 4.

	7. For women of childbearing potential (WOCBP) [see definition in Section 5.5]: • Negative serum pregnancy test at Visit 1; and • Agreement to undertake monthly urine or serum pregnancy tests during the study and up to the EOS visit; and • Agreement to use an acceptable contraceptive method as described in Section 5.5.2. 8. Able to speak, read and understand English, to communicate well with the investigator, to understand the study requirements, and judged by investigator to be alert and oriented to person, place, time, and situation. **Criteria assessed at Visit 2:** 9. Reporting ≥ 3 BE days for each of the 2 weeks prior to randomization as documented in the participant's BE diary and with BE diary entries completed for at least 6 days per week during this 2-week period (between Visit 1 and 2). 10. CGI-S score of ≥ 4. 11. For WOCBP: negative urine pregnancy test.
EXCLUSION CRITERIA	Study participants must not meet any the following exclusion criteria: **Criteria assessed at Visit 1:** 1. Body mass index (BMI) < 18.0 kg/m^2 or > 45 kg/m^2. 2. Any acute or chronic-persistent psychiatric disorder (see also under 3 and 4 below) other than BED diagnosed in the past, including anorexia nervosa, bulimia, psychotic disorders, bipolar disorder, hypomania, or dementia, as defined by the DSM-5 criteria or by the Mini International Neuropsychiatric Interview© (MINI©). 3. Episode(s) of major depressive disorder or any anxiety disorder occurring within the 6 months prior to Screening as defined by the DSM-5 criteria or by the MINI©; or currently

	taking, or has taken, any medication for depression or anxiety during the 3 months prior to Screening. 4. History of substance use disorder (including alcohol use disorder), excluding nicotine and caffeine, within the 12 months prior to Screening, as defined by the DSM-5 criteria or by the MINI©. 5. Any clinically unstable medical condition, significant medical disorder or acute illness that, in the investigator's opinion, could interfere with the participants ability to comply with study assessments or abide by study restrictions. 6. History of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer. History of pituitary tumor, whether benign or malignant, is exclusionary. 7. Presence of significant psychosocial or environmental stressors (e.g., loss of employment, loss of housing) or any factor that could impede participant's ability to adhere to protocol requirements, as judged by the investigator. 8. Participants whose work requires them to operate heavy-duty vehicles or other heavy or dangerous machinery. *Note: Participants must be cautioned on the potential risk of somnolence and it is recommended to refrain from engaging in hazardous activities that require complete mental alertness, including driving, following study treatment intake until fully alert and comfortable to do so [see also Section 5.7].* 9. Use of any medications for the treatment of BED (including lisdexamfetamine [Vyvanse®]), any other eating disorder, obesity, or weight gain, or any other medication that could result in weight gain or weight loss, including over-the-counter and herbal products, within 3 months prior to Screening. 10. Any ECG findings of corrected QT interval (QTc) prolongation or history of additional risk factors for torsade de pointes, which, in the opinion of the investigator, could

	affect the participant's safety or interfere with the study assessments. 11. Any abnormal hematology or biochemistry test results, which, in the opinion of the investigator, could affect the participant's safety or interfere with the study assessments. 12. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 × upper limit of normal (ULN) and/or total/direct bilirubin > 1.5 × ULN and/or moderate to severe hepatic impairment defined as Child-Pugh Score B or C. 13. Positive test for either hepatitis B surface antigen or hepatitis C antibody and AST and/or ALT and/or total bilirubin test results at Screening above the ULN for the reference laboratory. 14. Positive HIV test. 15. Thyroid-stimulating hormone (TSH) level outside of the established reference range to an extent that is considered clinically relevant per investigator judgment. Participants diagnosed with hyper- or hypothyroidism who have been on therapy with a stable dose for at least 3 months prior to Visit 1 and are clinically and chemically euthyroid are allowed. 16. Current or previous participation in any clinical trial within the last 90 days, or participation in more than 2 clinical trials within the past year. This includes studies using marketed drugs or devices. 17. Psychological or behavioral weight-loss interventions for BED initiated during the 3 months prior to Screening or planned to be initiated during the study. A participant treated with those therapies is eligible if the therapy has been started at least 3 months prior to randomization and the participant agrees to keep it stable during the study. 18. Any history of bariatric surgery including gastric jejunal bypass, Roux-en-Y gastric bypass, sleeve gastrectomy, lap

	bands, duodenal stents, or other procedures for weight loss or planned to be performed during the study. 19. Treatment with central nervous system (CNS)-active drugs, such as centrally active anticholinergics, sedating antihistamines, morphine and other opioids, anticonvulsants, antidepressants, anxiolytics, mood stabilizers, antipsychotics, stimulants, sleep drugs, anti-Parkinson's drugs, etc., within 30 days prior to Screening or planned to be initiated during the study. 20. Treatment with sensitive substrates of CYP3A4, moderate or strong inhibitors and/or inducers of CYP3A4, and sensitive substrates of CYP2C19, CYP2C8 and CYP2C9 within 2 weeks of randomization (Visit 2) or planned to be initiated during the study. 21. Consumption of the following fruits and their juices is not permitted within 2 weeks of randomization (Visit 2) to EOT visit: grapefruit, grapefruit hybrids, Seville orange, pomelos, pomegranates, and star fruits. 22. Use of medications that affect body weight or appetite, including weight loss medications, insulin, glucagon-like peptide-1 (GLP-1) receptor agonists, systemic corticosteroids, over-the-counter (including herbal) medications, within 3 months prior to Screening or planned to be initiated during the study. 23. Known hypersensitivity to drugs of the same chemical or pharmacological class as ACT-539313, or any of its excipients. 24. Previous exposure to ACT-539313. **Criteria assessed at Visit 1 and Visit 2** 25. HAMD-17 score ≥ 17 points at Visit 1 and/or Visit 2. 26. Any of the following conditions related to suicidality: a) Participant is considered to have a suicide risk in the investigator's opinion or has a previous history of suicide attempt within the past 12 months.

	b) Participant answers "yes" to "suicidal ideation" item 2 (non-specific active suicidal thoughts), item 3 (active suicidal ideation with any methods [not plan] without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan), or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS© assessment at Screening (in the past month). Participants who answer "yes" to this question must be referred to the investigator for follow-up evaluation. 27. Female participants: pregnant, lactating or planning to become pregnant during the projected course of the study. 28. Positive urine drug screen (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine, antidepressants, or cocaine).
STUDY TREATMENTS	ACT-539313 as capsules at a strength of 100 mg, taken orally, b.i.d. in the morning at breakfast and in the evening at dinner, with a glass of water (approx. 240 mL / 8 fl. oz.), during the treatment period. Matching placebo as identical capsules indistinguishable from ACT-539313, taken orally, b.i.d. in the morning at breakfast and in the evening at dinner, with a glass of water (approx. 240 mL / 8 fl. oz.), during the treatment period.
STATISTICAL METHODOLOGY	**Analysis sets** The Full analysis set (FAS) includes all participants who were randomized, received at least one dose of study treatment, and have a baseline assessment of the primary endpoint. The Per-protocol analysis set (PPS) includes all participants from the FAS without protocol deviations that potentially affect the primary endpoint (to be defined in the statistical analysis plan). The Safety analysis set (SAF) includes all randomized participants who received at least one dose of study treatment. Participants will be evaluated according to the study treatment they received.

Statistical hypotheses

The null hypothesis (H_0) is that there is no difference between ACT-539313 and placebo mean change from baseline to Week 12 in the number of BE days per week.

This hypothesis will be tested at a two-sided 0.05 level vs the alternative hypothesis that there is a difference between treatment groups.

Analysis of the primary efficacy variable

The primary analysis will be performed on the FAS. The primary estimand is a hypothetical strategy estimand. Changes from baseline to post-baseline time points in the number of BE days per week will be analyzed using a mixed model for repeated measurements with factors for treatment group, sex, BMI category and time point (Weeks 1–2, 3–4, 5–6, 7–8, 9–10, and 11–12), treatment by time interaction, and covariates for baseline number of BE days per week and the interaction between baseline and time point. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same participant. H_0 will be tested using the difference in least squares mean (LSMean) changes from baseline to Weeks 11–12. The null hypothesis will be rejected if the 95% confidence interval around this difference excludes zero. The analysis will also be evaluated in the PPS. Supplementary estimands are defined in the core text of this protocol.

Safety analyses

All safety analyses will be performed on the SAF. Adverse events, laboratory data, vital signs and ECG data will be summarized by treatment group using descriptive statistics. Daytime sleepiness is defined daily as any score > 3 on the SSS after the morning dose. It will be collected on Days 1–14 and expressed as a number of days per week. The mean number of days with daytime sleepiness per week will be summarized by treatment group.

Interim analysis

No interim analysis is planned.

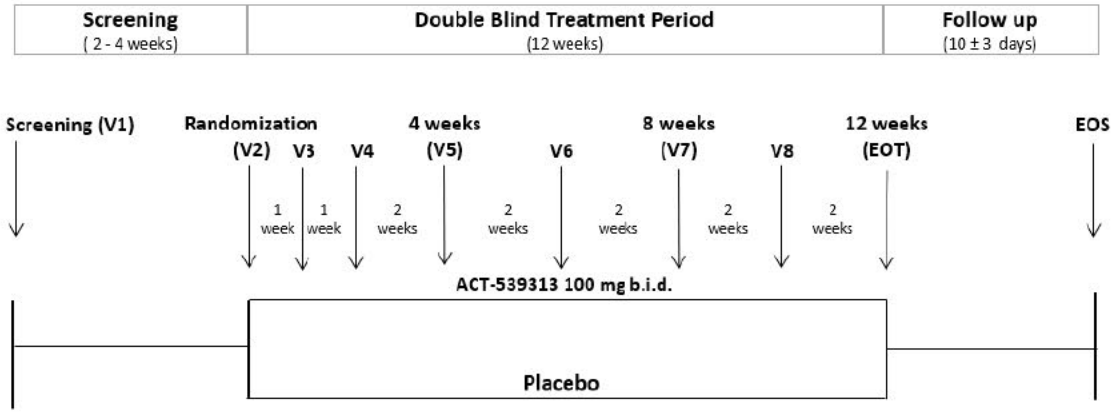
	Sample size The sample size is based on the primary efficacy endpoint. It is anticipated that a treatment group difference of 1 BE day per week (corresponding to an effect size of 0.5 to 0.7, depending on the standard deviation [SD]) is clinically meaningful as demonstrated in recent studies. The sample size needed for 90% power to detect an effect size of 0.6 is 120 participants (60 participants per arm). Such a sample size would also provide 78% power to detect a smaller effect size of 0.5.

The associated estimands [ICH 2020] are given in Section 9.2.

1.2 Scheme

The overall study design is depicted in Figure 1.

Figure 1 Study design



b.i.d. = twice daily; EOT = End-of-Treatment; EOS = End-of-Study; V = visit.

1.3 Schedule of activities

The visit schedule and protocol-mandated activities are performed according to the schedule of activities [Table 1] and are described in Section 7.

Table 1 Schedule of activities

PERIODS	Name	SCREENING	TREATMENT								FOLLOW-UP	UNSCHEDULED
	Duration	2–4 weeks	12 weeks								7–13 days	NA
VISITS	Number	1	2	3	4	5	6	7	8	EOT	EOS	U1
	Name	Screening	Randomization	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 / End-of-Treatment[8]	End-of-Study visit	Unscheduled visit[9]
	Time window	Day –28 to Day –1	Day 1	Day 8 (±1)	Day 15 (±2)	Day 29 (±2)	Day 43 (±2)	Day 57 (±2)	Day 71 (±2)	Day 85 (±2) or 1 to 5 days after last dose if premature EOT	10 ± 3 days after EOT	Any day between ICF signature and EOS
Signature of Informed consent form		X										
Eligibility		X	X									
Demographics		X										
Medical history		X										
Previous/concomitant therapy		X	X	X	X	X	X	X	X	X		
Physical examination		X								X		
Body weight and height[1]		X	X	X	X	X	X	X	X	X		
Vital signs (BP, PR, RR, T°)		X	X	X	X	X	X	X	X	X		(X)[9]
12-lead ECG (central)		X								X		(X)[9]
Hematology / blood chemistry[2]		X				X		X		X		(X)[9]
Serum/urine pregnancy test[3]		X	X			X		X		X	X	(X)[9]
Thyroid function		X										
Urine drug screen		X	X	X	X	X	X	X	X	X		
Viral serology		X										
PK sampling[4]						X		X		X		
Binge eating diary completion		◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►		
Stanford Sleepiness Scale[10]			◄	- - -	- - -	- - ►						
Binge eating diary check			X	X	X	X	X	X	X	X		
YBOCS-BE			X			X		X		X		
PGI-S			X			X		X		X		

PERIODS	Name	SCREENING	TREATMENT								FOLLOW-UP	UNSCHEDULED
	Duration	2–4 weeks	12 weeks								7–13 days	NA
VISITS	Number	1	2	3	4	5	6	7	8	EOT	EOS	U1
	Name	Screening	Randomization	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 / End-of-Treatment[8]	End-of-Study visit	Unscheduled visit[9]
	Time window	Day –28 to Day –1	Day 1	Day 8 (±1)	Day 15 (±2)	Day 29 (±2)	Day 43 (±2)	Day 57 (±2)	Day 71 (±2)	Day 85 (±2) or 1 to 5 days after last dose if premature EOT	10 ± 3 days after EOT	Any day between ICF signature and EOS
CGI-S		X	X			X		X		X		
CGI-C / PGI-C				X		X		X		X		
C-SSRS©		X	X	X	X	X	X	X	X	X	X	
MINI©		X										
SCID-5		X										
EDE-Q [5]		X	X			X		X		X		
HAMD-17		X	X				X			X	X	
BWSQ										X	X	
[redacted]												
Contact IRT		X	X	X	X	X	X	X	X	X		
Study treatment dispensing/return			X	X	X	X	X	X	X	X		
IMP capsule count				X	X	X	X	X	X	X		
Study treatment intake			◄----	----	----	----	----	----	----	----►		
AEs/SAEs/Procedures[7]		◄----	----	----	----	----	----	----	----	----	----	----►

1. Height only measured at Visit 1.
2. A central laboratory will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits. Blood samples will be drawn under fasted condition.
3. For WOCBP, serum test (central laboratory) at Visit 1 and EOT, urine test (performed locally) at Visit 2, Visit 5, Visit 7 and EOS. If urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
4. PK pre-dose assessment in the morning. Study participant to be instructed to withhold the morning dose until blood samples are drawn. Time of sample collection will be recorded in the eCRF.
5. EDE-Q full (28-item) version will be applied at Visit 1 and the brief (7-item) version EDE-Q7 at all other visits.

[redacted]

7. All AEs, SAEs and procedures that occur after signing the ICF and up to EOS must be reported.
8. All participants will be asked to return for an EOT visit. For participants who prematurely discontinue study treatment, the EOT visit will occur within 5 days of the last intake of study treatment. For participants who complete the treatment period as planned, the Week 12 visit corresponds to the EOT visit.
9. During unscheduled visits, additional assessments may be performed at the discretion of the investigator. The assessments in brackets are recommended to be performed on an unscheduled visit, based on medical judgment.
10. Stanford Sleepiness Scale to be filled in for the first 2 weeks of study treatment, twice daily, at breakfast (before morning dose) and around midday, prior to lunch time.

AE = adverse event; BP = blood pressure; BWSQ = Benzodiazepine Withdrawal Symptom Questionnaire; CGI-C = Clinical Global Impression of Change scale; CGI-S = Clinical Global Impression of Severity scale; C-SSRS© = Columbia Suicide Severity Rating Scale©; eCRF = electronic Case Report Form; ECG = electrocardiogram; EDE-Q: Eating Disorder Examination Questionnaire; EOS = End-of-Study; EOT = End-of-Treatment; HAMD-17 = Hamilton Rating Scale for Depression (17-item); ICF = informed consent form; IMP = Investigational Medicinal Product; IRT = Interactive Response Technology; MINI© = Mini International Neuropsychiatric Interview©; NA = not applicable; [redacted] PGI-C = Patient Global Impression of Change scale ; PGI-S = Patient Global Impression of Severity scale; PK = pharmacokinetic(s); PR = pulse rate; RR = respiratory rate; SAE = serious adverse event; SCID-5 = Structured Clinical Interview for DSM-5; T° = temperature; U1 = unscheduled visit; V = visit; WOCBP = women of childbearing potential; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating.

2 INTRODUCTION

ACT-539313 is being developed for the treatment of BED.

2.1 Binge eating disorder

2.1.1 Definition

BED is characterized by recurrent episodes of BE, i.e., eating episodes that occur in a discrete period of time (≤ 2 hours) and involve the consumption of an amount of food that is definitely larger than most people would consume under similar circumstances [APA 2013]. Other core features of BED include a sense of lack of control over eating during binge episodes, significant psychological distress (e.g., shame, guilt, embarrassment) about BE, and the absence of recurrent inappropriate compensatory behaviors such as purging, fasting, and excessive exercise.

In 2013, the APA recognized BED as a distinct eating disorder in the DSM-5 [APA 2013], whereas it was previously considered only a provisional diagnosis in DSM-IV. The key difference in the diagnostic criteria is the reduction of the required minimum average frequency and duration of BE from at least 2 days a week for 6 months (DSM-IV) to at least 1 day a week for 3 months (DSM-5).

The population prevalence of BED ranges between < 1% and 3.5% [Hudson 2007, Kessler 2013, Mustelin 2015, Preti 2009, Smink 2014]. The 12-month prevalence of BED (using DSM-5 diagnostic criteria) in the US population has been estimated at 1.6%, with a lifetime prevalence of 2.0% [Cossrow 2016].

BED is usually first diagnosed in young adulthood (early to mid-20s) [Kessler 2013, Stice 2013] and symptoms may persist in midlife and old age [Guerdjikova 2012].

2.1.2 Current treatment options

Treatment for BED includes a variety of approaches targeting the core behavioral features and psychological features of the disease. Psychological and behavioral approaches remain the mainstay of therapy and include cognitive behavioral therapy, interpersonal psychotherapy, and behavioral weight loss [Wilson 2011, Iacovino 2012, Steinberg 2014]. In January 2015, lisdexamfetamine became the first medication to receive US FDA approval for treating moderate to severe BED [Vyvanse® USPI]. Many other medications are used off-label, including antidepressants (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and bupropion), anticonvulsants (topiramate), and anti-obesity agents [McElroy 2017a, Citrome 2019].

2.1.3 Unmet medical need in BED

Patients with BED have significant functional impairment, decreased quality of life and psychiatric (primarily anxiety and mood disorders) as well as medical comorbidities, including obesity, type 2 diabetes and sleep problems [Kornstein 2017, Bellows 2015, Ling 2017].

While psychological and cognitive behavioral interventions have been recommended as first-line treatment [Hilbert 2017] and are supported by meta-analytic reviews, these treatments require specialized expertise and are often not widely available and/or costly. Furthermore, about 50% of patients with BED do not fully respond to psychological or behavioral treatments [Linardon 2018]. Currently available pharmacologic treatments, including those used off-label, are limited by unfavorable side effects. The CNS stimulant lisdexamfetamine (available in the US and Australia) is an amphetamine derivative with a significant abuse potential and is associated with cardiovascular adverse effects [Vyvanse® USPI].

2.2 ACT-539313

ACT-539313 is a selective, orally available, and brain-penetrating OX1R antagonist. Orexin neuropeptides regulate feeding behavior, compulsive reactions, stress processing, and the motivation for obtaining rewards through activation of OX1R, as well as sleep and wakefulness through OX2R.

ACT-539313 demonstrated reduction of compulsive eating of highly palatable food in rats where binge-like eating behavior was induced by prior dieting and stress. ACT-539313 will be evaluated as a novel medication for the treatment of BED.

The human clinical experience with ACT-539313 consists of a single-center, double-blind, randomized, placebo-controlled, single- and multiple-ascending doses, and exploratory pharmacodynamic Phase 1 study (AC-082-101) and a single-center, randomized, open-label, DDI study on CYP3A4 inhibition (ID-082-102). ACT-539313 was well tolerated at single oral doses of up to and including 400 mg and at multiple oral doses of up to and including 200 mg b.i.d. for 10 days.

Data from pharmacodynamic assessments showed signs of CNS activity but did not suggest any marked signs of reduced alertness, fatigue, or somnolence. Saccadic peak velocity decreased in a statistically significant manner following single-dose administration of 200 mg and 400 mg ACT-539313 when compared to placebo. Neither SAEs nor AEs leading to study treatment or study discontinuation were reported in the Phase 1 studies. The most frequently reported AEs were somnolence (SAD: 5/40 subjects [12.5%] and MAD: 4/28 subjects [14.3%]), dizziness (MAD: 2/28 subjects [7.1%]) and headache (SAD: 3/40 subjects [7.5%] and MAD: 2/28 subjects [7.1%]). In the MAD part of the study, reporting of somnolence increased with dose and was not observed in subjects

treated with placebo, whereas one subject on placebo reported headache (1/28 subjects [3.6%]).

More detailed information can be found in the IB [ACT-539313 IB].

2.3 Study rationale

The proposed effect of ACT-539313 on BED is based on its antagonism of OX1R. Recent studies have corroborated the primary role of orexins in compulsive, binge-like feeding behaviors in rodents [Merlo Pich 2014, Alcaraz-Iborra 2015]. OX1R antagonists reduced binge-like eating behavior in rat models [Piccoli 2012,Vickers 2015]. Another study showed that an OX1R antagonist could also inhibit the binge-like intake of sucrose and saccharin in mice [Alcaraz-Iborra 2014].

In nonclinical studies, ACT-539313 reduced compulsive binge eating-like behavior in a rat model of BE.

In the Phase 1 studies, ACT-539313 was well tolerated at single oral doses of up to and including 400 mg and at multiple oral doses of up to and including 200 mg b.i.d. for 10 days in studies in healthy subjects. This POC study will investigate the potential of ACT-539313 to show similar effects on BED in humans and will assess its impact on core behavioral features of the disease.

2.4 Benefit/risk assessment

The benefits of ACT-539313 on BED are not yet known. This is the first clinical study to assess the efficacy of OX1R antagonism as a new mechanism of action in the treatment of BED. Results of studies in an animal model of binge eating support the expectation of a benefit in this disorder. BED currently has limited therapeutic solutions, which are not devoid of safety concerns.

ACT-539313 is a selective OX1R antagonist and human experience so far has been limited to healthy subjects. Based on the safety and tolerability findings in healthy subjects in the clinically completed SAD, MAD, and DDI studies [see further details in the ACT-539313 IB], ACT-539313 was well tolerated:

- At single oral doses of up to and including 400 mg and multiple oral doses of up to and including 200 mg b.i.d. for 6.5 days in healthy male and female subjects; and
- At single and multiple oral doses of 200 mg b.i.d. for up to 10 days in healthy male subjects, and when given concomitantly with a single dose of 2 mg midazolam.

Accumulation of ACT-539313 was observed after multiple-dose administration (AUC_τ measured on Day 4 or Day 7 divided by AUC_τ on Day 1) was in the range of 1.6- to

2.1-fold. Similar to single dose administration, AUC_{τ} was dose-proportional, while maximum plasma concentration was less than dose-proportional.

ACT-539313 is classified as a moderate inhibitor of CYP3A4 at 200 mg b.i.d. and may affect the PK of CYP3A4 substrates; concomitant use of sensitive CYP3A4 substrates is not allowed in the study. [redacted] Dose-related somnolence was reported in the MAD study (4/28, 14.3%) and was not observed in subjects treated with placebo. The dose of ACT-539313 selected for this Phase 2 trial for treating BED in humans aims at an exposure resulting in selective antagonism of OX1R, avoiding sleep induction. Nonetheless, potential safety risks from daytime somnolence will be mitigated by excluding from study participation those individuals whose work requires them to operate heavy machinery [see Section 5.4]. In addition, excessive daytime sleepiness following study drug intake will be regularly assessed until the ability to remain alert while taking the drug is established. Cautionary advice will be given by the investigator with respect to activities requiring complete mental alertness, including driving. Standard monitoring and reporting of AEs, including assessment of prespecified AEs related to somnolence will be put in place [see Section 8].

[redacted] Hematologic and hepatic variables were unaffected in the Phase 1 studies. Liver and hematology variables will be monitored in this study.

ACT-539313 is not teratogenic nor embryotoxic in rats and rabbits. However, not all reproductive toxicity studies of ACT-539313 have been performed at this stage; therefore, ACT-539313 may be given to WOCBP only when absence of pregnancy has been verified. WOCBP must use a highly effective method of contraception during treatment and for 1 month after end of study treatment [see Section 5.5].

More information about the known and expected benefits, risks, and anticipated AEs can be found in the IB [ACT-539313 IB].

It is the investigator's/delegate's responsibility to monitor the benefit/risk ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual study participant level, and to discontinue study treatment or the study if, on balance, he/she believes that continuation would be detrimental to the study participant's wellbeing. Provided the protocol is adhered to, exclusion criteria, careful observation, and medical management will minimize any associated risk in this study. Overall, the benefit/risk assessment supports the conduct of the proposed ID-082A201 study.

3 STUDY OBJECTIVES AND ENDPOINTS

The overall objective of this POC study is to evaluate the clinical efficacy, safety, and tolerability of ACT-539313 100 mg administered b.i.d. compared to placebo in adult patients with moderate to severe BED over a period of 12 weeks.

All the objectives and their related endpoints are listed in Table 2.

Table 2 Objectives and endpoints

Objectives	Corresponding endpoints
Primary efficacy objective	
To assess the efficacy of ACT-539313 in the treatment of BED	The primary endpoint is the change from baseline to Week 12 in the number of BE days per week. A "BE day" is defined as a day with at least one confirmed BE episode.
Exploratory efficacy objectives	
To assess the efficacy of ACT-539313 in the treatment of BED	• Change from baseline to Week 12 in the number of BE episodes per week. • Percentage of study participants without BE episodes during the last 4 weeks of the treatment period.
To assess the efficacy of ACT-539313 in decreasing disease-specific obsessive and compulsive symptoms	• Change from baseline to Week 12 in the total score of the YBOCS-BE. • Change from baseline to Week 12 in the subscale scores (compulsive/obsessive, restraint, control) of the YBOCS-BE.

Objectives	**Corresponding endpoints**
To assess treatment effect on anxiety and depressive symptoms	• Change from baseline to Week 6 and to Week 12 in the HAMD-17 total score. • Change from baseline to Week 6 and to Week 12 in the HAMD-17 subitems 10 and 11. • Change from baseline to Week 6 and to Week 12 in the HAMD-17 MPS score.
To assess treatment effect on attitudinal and behavioral dimensions of eating and overall symptomatology in BED	• Change from baseline to Week 12 in the EDE-Q7 global score and 3 subscales scores (dietary restraint, shape/weight overvaluation and body dissatisfaction). • CGI-C score at Week 12. • PGI-C score at Week 12. • Change from baseline to Week 12 in the CGI-S. • Change from baseline to Week 12 in the PGI-S.
To assess treatment effect on body weight and glucose levels	• Change from baseline to Week 12 in body weight. • Change from baseline to Week 12 in HbA1c.
[redacted]	[redacted]
Safety objectives	
To assess the safety of ACT-539313 in patients with BED	• TEAEs[a] defined as an AE occurring from the start of study treatment administration up to the EOS. • Treatment-emergent SAEs defined as an SAE occurring from the start of study treatment administration up to the EOS. • TEAEs[a] leading to premature discontinuation of the study treatment. • Treatment-emergent AESIs up to EOS. AESIs include AEs related to somnolence (defined by pre-specified terms) from the start of study treatment administration up to the EOS. • Occurrence of daytime sleepiness assessed by SSS from the start of study treatment administration up to Visit 4 (Week 2).

Objectives	Corresponding endpoints
	• Treatment-emergent marked laboratory abnormalities[b] from the start of study treatment administration to all assessed time points during the study. • Change in vital signs (systolic and diastolic blood pressure, temperature, respiratory rate, and pulse rate) from baseline to all assessed time points during the study. • Medically relevant ECG abnormalities[b] while on study treatment from baseline to all assessed time points during the study. • Occurrence of withdrawal symptoms upon treatment discontinuation, as measured by change between Week 12 / EOT and EOS visit in BWSQ total score and HAMD-17 total score. • Occurrence of suicidal ideation and/or behavior while on study treatment based on the C-SSRS© from baseline to all assessed time points during the study up to EOS.
Other exploratory objectives	
To assess the PK of ACT-539313	• ACT-539313 plasma concentrations prior to morning dosing at Week 4, Week 8, and Week 12.

[a] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from study treatment start up to EOS, whether or not considered by the investigator as related to study treatment).

[b] A treatment-emergent marked laboratory abnormality or medically relevant ECG abnormality is any marked laboratory abnormality or medically relevant ECG abnormality temporally associated with the use of study treatment (from study treatment start to all assessed time points during the study). The selection of marked/medically relevant abnormalities considered for the analyses will be based on standard definitions and described in the SAP.

AE = adverse event; AESI = adverse event of special interest; BE = binge eating; BED = binge eating disorder; CGI-C = Clinical Global Impression of Change scale ; CGI-S = Clinical Global Impression of Severity scale ; C-SSRS© = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EDE-Q7 = Eating Disorder Examination Questionnaire (7-item); EOS = End-of-Study; EOT = End-of-Treatment; HAMD-17 = Hamilton Rating Scale for Depression (17-item); FERT = Facial Expression Recognition Task; HbA1c = glycated hemoglobin; MPS = Maier-Philipp subscale; [redacted]PGI-C = Patient Global Impression of Change scale; PGI-S = Patient Global Impression of Severity; PT = preferred term; SAE = serious adverse event; SAP = statistical analysis plan; SSS = Stanford Sleepiness Scale: TEAE = treatment-emergent adverse event; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating

3.1 Efficacy endpoints

3.1.1 Primary efficacy endpoint

The primary efficacy endpoint of the study is the change from baseline to Week 12 in the number of BE days per week.

A "BE day" is a day in which at least one confirmed BE episode occurred [see Section 7.2.4.1].

A BE episode is defined as "eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances" (as defined in the DSM-5 criteria) [APA 2013]. In addition, a BE episode is characterized by "a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)".

Throughout the study, from Screening to Week 12, study participants record each BE episode they experience on a diary card that is filled in daily. At randomization and at each subsequent study visit, the investigator reviews the diary entries with the study participant to determine whether a recorded episode fulfilled criteria for a BE episode and to ascertain if there were other unrecorded BE episodes during the preceding interval. The investigator records in the eCRF the BE episodes that have been confirmed. In the eCRF, every day must be described as either having an entry (0 or x number of BE episodes) or not having an entry (missing data).

The "number of BE days per week at baseline" is calculated as the number of BE days from Day −14 to Day −1 divided by the number of days with diary entries in this period and multiplied by 7. A minimum of 6 entries for each of the 2 weeks preceding randomization is required per inclusion criteria to ensure study participant compliance with filling in the BE diary.

The "number of BE days per week" during the study, from randomization up to Week 12, is calculated as the number of BE days over a 2-week period divided by the number of days with diary entries in this period and multiplied by 7. A minimum of 7 diary entries per 14-day time interval is required [see Section 9.2.2.1]. The last calculation, covering Weeks 11 and 12, will be used for the primary endpoint.

All calculations will be done by the sponsor; the calculations at baseline should also be done by the investigator as part of the eligibility assessment, as per Section 7.2.3. The sponsor may collect the original diaries for data reconciliation.

3.1.2 Exploratory efficacy endpoints

Exploratory efficacy endpoints are listed in Table 2.

3.2 Safety endpoints

Safety endpoints are listed in Table 2.

3.3 Pharmacokinetic endpoints

ACT-539313 plasma concentrations will be measured prior to the morning dosing at Week 4, Week 8, and Week 12 to determine individual trough concentrations and the possible influence of various covariates thereupon. Population PK parameter estimates

may also be evaluated on an exploratory basis. Plasma samples may also be used by Idorsia Preclinical Pharmacokinetics and Metabolism department for exploratory assessments of circulating metabolites of ACT-539313.

3.4 Appropriateness of endpoints

The assessment of the change in the number of BE days per week as an endpoint has been accepted by the FDA, supporting approval of other therapies in this indication. The FDA review of the lisdexamfetamine dimesylate dossier [FDA 2015], discussing the adequacy of weight loss as primary endpoint in BED, did not consider weight loss as a suitable primary endpoint for this disease: "... primary efficacy endpoint is most important information for clinicians, and for patients with BED (reducing binge eating days), and so the emphasis in labeling should be on the psychiatric aspects of the disorder...".

A change in BED may be assessed either by a reduction in the frequency of BE episodes or by a reduction in the frequency of BE days. The frequency of BE episodes is a good descriptor of disease severity and it allows the reduction in severity for study participants not reaching remission to be assessed. In patients with severe BED, if the reduction in episode frequency is large enough it could lead to a meaningful benefit. With lisdexamfetamine dimesylate, treatment effects were observed consistently across several BE-related endpoints including BE episodes and BE days, reinforcing the clinical relevance of both endpoints [McElroy 2017b]. Similar conclusions were drawn in clinical trials with topiramate [McElroy 2007] and sibutramine [Wilfley 2008].

Attitudinal and behavioral dimensions of the eating psychopathology in BED will be assessed by the change from baseline to Week 12 in the EDE-Q 7-item scale global score and subscale scores on dietary restraint, shape/weight overvaluation, and body dissatisfaction.

BED shares many characteristics with addictive behaviors, e.g., diminished control, continued food intake despite negative consequences [Gearhardt 2012], and with obsessive-compulsive symptoms (or features) in that symptoms are intrusive, time consuming, distressing, potentially inhibit or hinder functioning, and may or may not be successfully resisted [Deal 2015]. The study will also assess the efficacy of the drug on disease-specific obsessive and compulsive symptoms by using the YBOCS-BE [Goodman 1989, Deal 2015].

The study will use the CGI-S/C as well as the PGI-S/C scales to assess the global impression of disease related to severity and change from a clinician and patient perspective.

Anxiety and depression are common comorbidities in BED [Guerdjikova 2017]; the study will use HAMD-17 to assess symptoms of anxiety and depression. [redacted]

[redacted]

In summary, all efficacy assessments have been well documented and regarded as reliable, accurate and relevant in this patient population.

4 STUDY DESIGN AND PLAN

4.1 Study design

This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study assessing ACT-539313 at a dosing regimen of 100 mg b.i.d. vs placebo over a 12-week treatment period in adult participants with moderate to severe BED.

The study treatment will be taken in the morning at breakfast and in the evening at dinner.

This study will randomize approximately 120 participants to either ACT-539313 at a dose of 100 mg b.i.d., or placebo in a 1:1 ratio.

4.1.1 Study periods for an individual study participant

The study comprises the following consecutive periods:

Screening period: Lasts a minimum of 14 days and up to 28 days; starts with the full signature (study participant, investigator/delegate) of the ICF and ends with the study participant's randomization or screening failure.

Treatment period: Starts with the administration of the first dose of study treatment and ends on the day of the last dose of study treatment. The study participants will be treated for 12 weeks.

Safety follow-up period: Starts on the day after the last dose of study treatment and ends at the EOS visit (10 ± 3 days after EOT).

Participation in the study ends with the completion of the EOS visit [Table 1]. The duration of participation in the study of a study participant is expected to be up to 128 days.

The visit schedule and protocol-mandated procedures are performed according to the schedule of activities [Table 1] and are described in Section 7.2.

The overall study design is depicted in Figure 1.

4.2 Study duration and global End-of-Study definition

The study starts with the recruitment of the first study participant. A study participant is considered recruited when the study participant's ICF has been fully signed.

The study primary completion date is the date of the last study participant's EOT visit.

The global EOS is defined as completion of the EOS visit of the last study participant. The study is expected to last approximately 14 months.

4.3 Study design rationale

The proposed clinical study ID-082A201 has been designed based on previously conducted clinical studies in BED [McElroy 2017b, Wilfley 2008, FDA 2015] as well as data from the two ACT-539313 Phase 1 studies, AC-082-101 [D-18.013, D-20.035] and ID-082-102 [D-18.159]. This is the first clinical study to assess selective OX1R antagonism as a new mechanism of action in patients with eating disorders and to establish an initial signal for efficacy and to ensure safety. Based on the results of this study, ACT-539313 may be further investigated in a Phase 2 dose-finding study and in a confirmatory Phase 3 program in BED.

The DB, randomized, and placebo-controlled design minimizes the chance of bias in the implementation, execution, assessment, and interpretation of the effects of treatment. While there is a drug approved for BED (lisdexamfetamine), its status as a Schedule II controlled substance limits its use in this POC study as an active control.

A treatment duration of 12 weeks has been selected as this duration has been adequate to evaluate the benefit/risk of compounds tested in this indication [McElroy 2017b, FDA 2015]. In addition, it is unclear how long it would take for an OX1R antagonist to modulate the neuronal dysregulation of BED, leading to a reduction in the compulsive behavior that will then translate into a reduction in BE episodes. The 12-week duration is expected to provide an adequate time period to allow for both efficacy and safety data assessment.

4.4 Justification for dose

For this POC study, the dose of 100 mg b.i.d. was chosen to assess the effect of ACT-539313 on BED.

The selected dose of 100 mg b.i.d. is expected to cover the exposure to ACT-539313 that was necessary in a rat model to reduce BE by selective OX1R antagonism. Safety pharmacology and toxicity studies have demonstrated appropriate safety margins, [redacted].

Single doses up to 400 mg and multiple doses up to 200 mg b.i.d. for 6.5 days have been tested in healthy male and female study participants, while a dose of 200 mg b.i.d. for up to 10 days has been tested in healthy male study participants. No safety issue of concern was detected as all AEs were transient and of mild or moderate intensity, and no

treatment-related effects on vital signs, clinical laboratory, or ECG variables were observed.

4.5 Study committee(s)

No study committee will be appointed for this study.

5 STUDY POPULATION

5.1 Study participant population description

This study will enroll male and female participants aged 18–55 years (inclusive), with a diagnosis of BED in accordance with DSM-5 criteria. In addition, the disease severity should be at least moderate, defined in this study as having at least 4 BE episodes per week, on average, for a duration of at least 6 months.

To ensure proper application of the diagnostic criteria, the BED diagnosis section of the SCID-5 will be used at Screening. This is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. In addition, the EDE-Q will be completed at Screening to further confirm the diagnosis of BED, assess all dimensions of the eating psychopathology, as well as confirm the self-reported BED severity.

More details on inclusion and exclusion criteria follow below [see Sections 5.3 and 5.4].

5.2 Rationale for the selection of the study population

The rationale for selecting patients with at least moderate severity and longer duration of BE symptoms (≥ 6 months) is that these patients are more likely to be impacted by the disease, more likely to seek treatment, and thus more likely to respond to the effects of a pharmacological intervention such as ACT-539313. In studies looking at both clinical and community samples, patients with moderate to severe BED, and especially those with overvaluation of weight/shape, were found to have greater eating-disorder psychopathology than patients with mild BED [Grilo 2015a, Grilo 2015b]. Patients with moderate to severe BED are often considered for pharmacotherapy as either monotherapy or in combination with behavioral treatment options.

Placebo response during clinical trials of medications for BED has been reported to range from 26% to 38%, with less severe eating pathology at baseline being associated with a higher placebo response [Blom 2014].

In comparison to other eating disorders, BED is distributed more broadly across age, sex, and racial/ethnic groups and no restrictions are made in this study with respect to these factors. However, in this initial POC study, an upper age limit of 55 years is included to increase the probability of detecting an efficacy signal as persistence of BED in older

individuals may be a sign of intractable BE and poorer response to treatment. Subsequent studies will allow a broader age range, beyond the 55 years limit.

5.3 Inclusion criteria

Study participants must meet all the following inclusion criteria:

Criteria assessed at Visit 1:

1. Signed and dated informed consent form prior to any study-mandated procedure.
2. Male or female study participants aged 18 to 55 years at the time of signing the informed consent form.
3. BED in accordance with DSM-5 criteria diagnosed using the SCID-5.
4. Self-reported BED severity of at least moderate level, defined as at least 4 BE episodes per week, on average, for a duration of at least 6 months.
5. BED in accordance with EDE-Q.
6. CGI-S score of ≥ 4.
7. For WOCBP [see definition in Section 5.5]:
   - Negative serum pregnancy test at Visit 1; and
   - Agreement to undertake monthly urine or serum pregnancy tests during the study and up to the EOS visit; and
   - Agreement to use an acceptable contraceptive method as described in Section 5.5.2.
8. Able to speak, read and understand English, to communicate well with the investigator, to understand the study requirements, and judged by investigator to be alert and oriented to person, place, time, and situation.

Criteria assessed at Visit 2:

9. Reporting ≥ 3 BE days for each of the 2 weeks prior to randomization as documented in the participant's BE diary and with BE diary entries completed for at least 6 days per week during this 2-week period (between Visit 1 and 2).
10. CGI-S score of ≥ 4.
11. For WOCBP: negative urine pregnancy test.

5.4 Exclusion criteria

Study participants must not meet any of the following exclusion criteria:

Criteria assessed at Visit 1:

1. BMI < 18.0 kg/m^2 or > 45 kg/m^2.
2. Any acute or chronic-persistent psychiatric disorder (see also under 3 and 4 below) other than BED diagnosed in the past, including anorexia nervosa, bulimia, psychotic disorders, bipolar disorder, hypomania, dementia, as defined by the DSM-5 criteria or by the MINI©.
3. Episode(s) of major depressive disorder or any anxiety disorder occurring within the 6 months prior to Screening as defined by the DSM-5 criteria or by the MINI©; or currently taking, or has taken, any medication for depression or anxiety during the 3 months prior to Screening.
4. History of substance use disorder (including alcohol use disorder), excluding nicotine and caffeine, within the 12 months prior to Screening, as defined by the DSM-5 criteria or by the MINI©.
5. Any clinically unstable medical condition, significant medical disorder or acute illness that, in the investigator's opinion, could interfere with the participant's ability to comply with study assessments or abide by study restrictions.
6. History of malignancy within 5 years prior to the Screening visit, except for adequately treated basal cell or squamous cell skin cancer. History of pituitary tumor, whether benign or malignant, is exclusionary.
7. Presence of significant psychosocial or environmental stressors (e.g., loss of employment, loss of housing) or any factor that could impede participant's ability to adhere to protocol requirements, as judged by the investigator.
8. Participants whose work requires them to operate heavy-duty vehicles or other heavy or dangerous machinery.

Note: Participants must be cautioned on the potential risk of somnolence and it is recommended to refrain from engaging in hazardous activities that require complete mental alertness, including driving, following study treatment intake until fully alert and comfortable to do so [See also Section 5.7].

9. Use of any medications for the treatment of BED (including lisdexamfetamine [Vyvanse®]), any other eating disorder, obesity, or weight gain, or any other medication that could result in weight gain or weight loss, including over-the-counter and herbal products, within 3 months prior to Screening.

10. Any ECG findings of QTc prolongation or history of additional risk factors for torsade de pointes, which, in the opinion of the investigator, could affect the participant's safety or interfere with the study assessments.

11. Any abnormal hematology or biochemistry test results, which, in the opinion of the investigator, could affect the participant's safety or interfere with the study assessments.

12. AST and/or ALT > 1.5 × ULN and/or total/direct bilirubin > 1.5 × ULN and/or moderate to severe hepatic impairment defined as Child Pugh Score B or C.

13. Positive test for either hepatitis B surface antigen or hepatitis C antibody and AST and/or ALT and/or total bilirubin test results at Screening above the ULN for the reference laboratory.

14. Positive HIV test.

15. TSH level outside of the established reference range to an extent that is considered clinically relevant per investigator judgment. Participants diagnosed with hyper- or hypothyroidism who have been on therapy with a stable dose for at least 3 months prior to Visit 1 and are clinically and chemically euthyroid are allowed.

16. Current or previous participation in any clinical trial within the last 90 days, or participation in more than 2 clinical trials within the past year. This includes studies using marketed drugs or devices.

17. Psychological or behavioral weight-loss interventions for BED initiated during the 3 months prior to Screening or planned to be initiated during the study. A participant treated with those therapies is eligible if the therapy has been started at least 3 months prior to randomization and the participant agrees to keep it stable during the study.

18. Any history of bariatric surgery including gastric jejunal bypass, Roux-en-Y gastric bypass, sleeve gastrectomy, lap bands, duodenal stents, or other procedures for weight loss or planned to be performed during the study.

19. Treatment with CNS-active drugs, such as centrally active anticholinergics, sedating antihistamines, morphine and other opioids, anticonvulsants, antidepressants, anxiolytics, mood stabilizers, antipsychotics, stimulants, sleep drugs, anti-Parkinson's drugs, etc., within 30 days prior to Screening or planned to be initiated during the study.

20. Treatment with sensitive substrates of CYP3A4, moderate or strong inhibitors and/or inducers of CYP3A4, and sensitive substrates of CYP2C19, CYP2C8 and CYP2C9 within 2 weeks of randomization (Visit 2) or planned to be initiated during the study.

21. Consumption of the following fruits and their juices is not permitted within 2 weeks of randomization (Visit 2) to EOT visit: grapefruit, grapefruit hybrids, Seville orange, pomelos, pomegranates, and star fruits.

22. Use of medications that affect body weight or appetite, including weight loss medications, insulin, GLP-1 receptor agonists, systemic corticosteroids, over-the-counter (including herbal) medications, within 3 months prior to Screening or planned to be initiated during the study.

23. Known hypersensitivity to drugs of the same chemical/pharmacological class as ACT-539313, or any of its excipients.

24. Previous exposure to ACT-539313.

Criteria assessed at Visit 1 and Visit 2

25. HAMD-17 score ≥ 17 points at Visit 1 and/or Visit 2.

26. Any of the following conditions related to suicidality:

    a) Participant is considered to have a suicide risk in the investigator's opinion or has a previous history of suicide attempt within the past 12 months.

    b) Participant answers "yes" to "suicidal ideation" item 2 (non-specific active suicidal thoughts), item 3 (active suicidal ideation with any methods [not plan] without intent to act), item 4 (active suicidal ideation with some intent to act, without specific plan), or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS© assessment at Screening (in the past month). Participants who answer "yes" to this question must be referred to the investigator for follow-up evaluation.

27. Female participants: pregnant, lactating or planning to become pregnant during the projected course of the study.

28. Positive urine drug screen (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine, antidepressants or cocaine).

5.5 Contraception requirements for women of childbearing potential

5.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Post-menopausal state is defined as 12 consecutive months with no menses without an alternative medical cause (ICH M3 definition).

5.5.2 Methods of contraception

WOCBP [see definition in Section 5.5.1] must use a highly effective contraceptive method from Screening visit up to 30 days after study treatment discontinuation.

Contraceptive methods with low user dependency should preferably be used, particularly when contraception is introduced as a result of participation in the study.

Highly effective contraceptive methods are defined as those, alone or in combination, that result in a failure rate of less than 1% per year when used consistently and correctly. Such methods include:

1. Hormonal contraceptives: Combined (containing estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation using one of the following routes of administration:
   a. Oral
   b. Intravaginal
   c. Transdermal
   d. Injectable
   e. Implantable (low user dependency)

   If a hormonal contraceptive is chosen from this group, it must be taken for at least 30 days prior to administration of the first study treatment dose. If during the study treatment period a study participant switches, or starts, a hormonal contraceptive method, additional contraceptive protection may be required to ensure a highly effective contraceptive method is used without discontinuation.

   Hormonal contraception from the above list must be used in conjunction with a supplemental barrier. The acceptable supplemental barrier methods to be used in conjunction with hormonal contraception are: male condom (preferred method), female condom, cervical cap, or diaphragm. Cervical cap and diaphragm must be used in combination with a spermicide. In countries in which spermicides are not available/authorized, cervical cap and diaphragm must not be used.
2. Intrauterine device (low user dependency).
3. Intrauterine hormone-releasing system (low user dependency).
4. Bilateral tubal occlusion/ligation at least 6 weeks prior to Screening visit (low user dependency).

5. Vasectomized partner; this is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
6. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment(s). The reliability of sexual abstinence needs to be evaluated in relation to: the duration of the clinical study; whether it is the preferred and usual lifestyle of the study participant; and whether it is locally accepted as a highly effective method of contraception.

The following contraception schemes used alone are NOT considered as highly effective methods of contraception:

- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with or without spermicide.

The following methods are NOT ALLOWED as methods of contraception for this study:

- Progestogen-only oral hormonal contraception (except if inhibition of ovulation is the primary mode of action).
- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides only.
- Lactational amenorrhea method.
- Combination of female condom and male condom.

If the investigator/delegate finds that the protocol-mandated highly effective method of contraception is not consistently and correctly followed by the study participant, the study treatment **must** be permanently discontinued [see Section 5.9.1.2].

Note: The documentation of method of contraception can be based on the site personnel's review of the study participant's medical records, medical examination, or medical history interview of the study participant.

5.6 Contraception for male study participants with WOCBP partner

No contraceptive methods are needed for male study participants participating in this clinical study.

5.7 Dietary aspects and physical activity restrictions

During the study, study participants will be instructed to:

- Refrain from consumption of grapefruit, grapefruit hybrids, Seville orange, pomelos, pomegranates, and star fruits, and their juices from 2 weeks before the start of study treatment until the last dose of study treatment.
- Abstain from strenuous exercise before each blood collection for clinical laboratory tests.
- Refrain from consuming alcohol > 2 drinks a day.
- A drink is defined as:
  a. A bottle/can of 33 cl / 12 ounces of beer (≈14 grams alcohol)
  b. A glass of 10–12 cl / 4 ounces of wine (≈12 grams alcohol)
  c. A small glass of 3–4 cl / 1 ounce of liquor (≈9 grams alcohol)
- Refrain from engaging in hazardous activities that require complete mental alertness, such as driving or operating heavy machinery, following study treatment intake until fully alert and comfortable to do so.

5.8 Screen failures and re-screening

Screen failures are defined as participants recruited in the clinical study (i.e., ICF fully signed) but not subsequently enrolled in the study. Minimum information includes demography, medical history, screen failure details (i.e., reason for screen failure), BE diary data, concomitant medication, adverse events and eligibility criteria not met.

It is not permitted to re-screen study participants in this study.

5.9 Criteria for withdrawal of study participants

A study participant has the right to prematurely discontinue study treatment at any time, by withdrawing from study treatment only or by withdrawing from study treatment and any further participation in the study (i.e., premature withdrawal from the study). It is recommended that the investigator/delegate makes a reasonable effort to maintain study participants on treatment, as medically appropriate, and follow the schedule of visits, since data robustness depends on such compliance. Should a study participant stop treatment or withdraw from the study, the investigator/delegate should ascertain the reason(s), while fully respecting the study participant's rights.

Study participants who prematurely discontinue study treatment, or the study, for any reason will not be replaced.

5.9.1 Study treatment premature discontinuation

The decision to prematurely discontinue study treatment may be made by the study participant, the investigator/delegate, or the sponsor personnel.

The investigator/delegate has the option of prematurely discontinuing study treatment for a given study participant in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. If study treatment is interrupted by the study participant for any reason, she/he must inform the investigator/delegate as soon as possible. Study treatment dose interruptions must be recorded in the eCRF.

The investigator/delegate must permanently discontinue study treatment for a given study participant if, on balance, he/she believes that continued administration would be contrary to the best interests of the study participant.

Study-specific criteria for permanent discontinuation of study treatment are described in Sections 5.9.1.1 to 5.9.1.4.

The main reason for permanent discontinuation of study treatment (e.g., due to pre-specified study treatment discontinuation criteria, an AE, lack of efficacy, study termination) must be documented in the eCRF.

A study participant who prematurely discontinues study treatment is not considered as withdrawn from the study.

The study participant who prematurely discontinues study treatment or who is permanently discontinued from study treatment will be asked to return for an EOT visit within 1 to 5 days of last intake of study treatment and thereafter to attend follow-up visits as defined in the schedule of activities [Table 1, Section 7.2].

5.9.1.1 Pregnancy

If a study participant becomes pregnant while on study treatment, study treatment must be permanently discontinued. The investigator/delegate must counsel the study participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. For reporting of pregnancies, refer to Section 8.3.1.

5.9.1.2 Lack of compliance with methods of contraception

If the investigator/delegate considers that the study participant is not compliant with the protocol instructions on methods of contraception; study treatment must be permanently discontinued.

5.9.1.3 Liver aminotransferase abnormalities

If ALT or AST $\geq 3 \times$ ULN and $< 8 \times$ ULN, a re-test of aminotransferases, total and direct bilirubin, and alkaline phosphatase must be performed within 7 calendar days. If the aminotransferase values return to pre-treatment levels or within normal ranges, study treatment can be continued. If AST or ALT elevation is confirmed, study treatment must be stopped and not re-introduced. Aminotransferases, total and direct bilirubin, and

alkaline phosphatase levels must be monitored at least once every 7 calendar days until values return to pre-treatment levels or within normal ranges.

Study treatment must be stopped, and its reintroduction is not to be considered in the following cases:

- Aminotransferases ≥ 8 × ULN
- Aminotransferases ≥ 3 × ULN and associated clinical symptoms of liver injury, e.g., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever)
- Aminotransferases ≥ 3 × ULN and associated increase in total bilirubin ≥ 2 × ULN

Aminotransferases, total and direct bilirubin, and alkaline phosphatase levels must be monitored at least once every 7 calendar days after study treatment discontinuation until values return to pre-treatment levels or within normal ranges.

Furthermore, other diagnoses (e.g., viral hepatitis, mononucleosis, toxoplasmosis, cytomegalovirus, alcoholic hepatitis, non-alcoholic steatohepatitis, autoimmune disease) and/or etiologies (e.g., hepatic toxicity of concomitant medication[s] or other substances) should be considered and ruled out by performing the appropriate tests.

All liver aminotransferases abnormalities leading to study treatment discontinuation must be recorded as AEs [see Section 8.1.1].

5.9.1.4 COVID-19

Provisions for study participants infected with SARS-CoV-2 or quarantined due to pandemic

Testing for SARS-CoV-2 should follow local guidance. Mandatory testing is not required for this study; however, standards for testing and management should be followed according to local and site-specific guidelines.

Should a study participant become infected with SARS-CoV-2 / contract COVID-19, or should a study participant be quarantined:

- Information about COVID-19 infection, whether positively confirmed with a SARS-CoV-2 test or not, and its corresponding diagnosis (including pneumonia related to COVID-19), symptoms, as well as administered medications, will be collected on the AE and Concomitant Medication pages of the eCRF.
- If a study participant is without symptoms and remains asymptomatic, study treatment can be continued as per protocol.

- If a study participant presents with mild symptoms, study treatment can be continued as per protocol and the study participant should be closely monitored. Should the symptoms worsen, study treatment may be discontinued as per investigator judgment.
- If a study participant develops severe symptoms or requires hospitalization for COVID-19, the study participant must be discontinued from study treatment.
- When shipping blood samples from study participants who tested positive or have a high potential to test positive for SARS-CoV-2 virus infection to the study central laboratory, the central laboratory manual and the most up-to-date COVID-19 regional guidance should be followed.
- DDI with medications used to treat COVID-19: Certain treatments used for COVID-19, such as lopinavir/ritonavir (strong CYP3A4 inhibitor) are contraindicated in association with ACT-539313. Please refer to the IB for more details on potential DDIs with ACT-539313. If possible, such treatments should be avoided for at least 24 hours after the last dose of study treatment. Details of any medication given for COVID-19 management should be recorded in the eCRF under Concomitant medications.

COVID-19 vaccination

COVID-19 vaccination with authorized vaccines, as per CDC and local guidelines, is allowed, provided the vaccination conditions set forth by the respective manufacturer (consistent with the respective prescribing information / package insert) are observed. Prior to any planned vaccination the study participant should, after consultation with his/her primary care physician, inform the investigator of such plan. Study visits and assessments should continue as planned if possible and appropriate as per investigator judgment. Receipt of the vaccine, and details thereof, should be recorded in the medical notes and in the eCRF under Concomitant medications.

General reporting of AEs should continue to be implemented as described in Section 8.2, including vaccination-related AEs, and reports of AEs for approved vaccines should be submitted as appropriate to the Vaccine Adverse Events Reporting System (VAERS) as per FDA guidance [FDA 2021].

5.9.2 Withdrawal from the study

Study participants may voluntarily withdraw from the study without justification for any reason at any time. Study participants are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up [see Section 5.9.3]. If a study participant withdraws consent for further study participation, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator/delegate may withdraw a study participant from the study (without regard to the study participant's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of

the study participant. Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study [see Section 10.10].

Enrolled study participants who prematurely discontinue from the study for any reason will not be replaced.

If, for whatever reason (except death or loss-to-follow-up), a study participant is withdrawn from the study, the investigator/delegate should make best efforts to schedule a last appointment / telephone call to assess the safety and well-being of the study participant, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the study participant's medical records, but they will not be collected in the eCRF.

The main reason for premature withdrawal from the study must be documented in the eCRF.

The investigator must provide follow-up medical care for all study participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 6.3.

5.9.3 Loss to follow-up

A study participant will be considered as lost to follow-up if he/she repeatedly fails to return for scheduled visits and cannot be contacted by the site.

The site must take preventive measures to avoid a study participant being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted if the study participant cannot be reached).

The following actions must be taken if a participant fails to return to the site for a scheduled study visit:

- The site staff must attempt to contact the study participant and reschedule the missed visit as soon as possible and counsel the study participant on the importance of maintaining the assigned visit schedule and ascertain if the study participant wishes to and/or should continue in the study.
- If the study participant cannot be reached, the site must make a reasonable effort to contact the study participant and document all attempts in the study participant medical chart. Reasonable efforts include, where possible, three telephone calls to the last available telephone number and one registered/certified letter to the study participant's last known mailing address or local equivalent methods.
- If the study participant is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

The date of last contact with the study participant will be collected in the eCRF.

6 TREATMENTS

6.1 Study treatment

6.1.1 Investigational treatment and matching placebo description

ACT-539313 is supplied by the sponsor as capsules at a strength of 100 mg. Matching placebo will be supplied by the sponsor as identical capsules indistinguishable from ACT-539313.

6.1.2 Study treatment dosing and administration

ACT-539313 or matching placebo will be available as capsules at a strength of 100 mg, taken orally, b.i.d. in the morning at breakfast and in the evening at dinner with a glass of water (approx. 240 mL / 8 fl. oz.), during the treatment period.

On study visit days when blood samples will be collected, participants will be asked not to take their morning dose until blood samples are drawn.

6.1.2.1 Study treatment dose adjustments

Study treatment dose adjustments are not permitted.

6.1.3 Treatment assignment

A total of approximately 120 study participants will be randomized in a 1:1 ratio to ACT-539313 or placebo. Randomization will not be stratified.

After verifying that the study participant meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system at Visit 2 to randomize the study participant. The IRT assigns a randomization number to the study participant and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number.

The IRT system is handled by an external independent vendor who will generate the randomization list.

6.1.4 Blinding

This study will be performed in a DB fashion. The investigator, site study personnel, the study participants, CRAs, sponsor personnel, and vendor/CRO personnel responsible of the conduct of the study, will remain blinded to the study treatment allocation until study database lock.

To ensure adequate supply of study treatment, the IRT vendor personnel responsible for clinical study distribution and the sponsor individuals contributing to clinical supply distribution will need to be unblinded at study participant level and depot level,

respectively. These persons will be clearly identified, their unblinding status will be documented in the trial master file and controlled as per sponsor/CRO procedures.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to IRT vendor and authorized persons (i.e. dedicated members of the Pharmaceutical Development group), who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

To minimize the possibility of systematic unblinding, the results of the PK data will not be communicated to the investigator, study personnel, study participants, CRAs, any sponsor or vendor/CRO personnel involved in the conduct of the study. Results will be transferred by the sponsor Bioanalytical Laboratory group (for PK data) to the sponsor and CRO personnel involved in the conduct of the study only after database lock.

6.1.5 Unblinding

6.1.5.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database lock, in accordance with the sponsor and/or the CRO's Quality System documents.

6.1.5.2 Unblinding for Independent Data Monitoring Committee or interim analyses

Not applicable.

6.1.5.3 Unblinding for suspected unexpected serious adverse reactions

If a SUSAR [see definition in Section 8.2.3] occurs for a study participant, sponsor's Global Drug Safety will perform unblinding of the treatment assignment for that study participant in order to meet regulatory reporting requirements.

Unblinded information will be accessible only to sponsor personnel who need to be involved in the safety reporting to the regulatory authorities and/or IECs/IRBs.

6.1.5.4 Emergency procedure for unblinding

The identity of the study treatment may be revealed only if the study participant experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator/delegate can receive the unblinded treatment assignment through the IRT.

In these situations, the decision to unblind resides solely with the investigator and must be clearly justified and explained. Whenever it is possible, and if it does not interfere with (or does not delay) any decision in the best interest of the study participant, the investigator is

invited to discuss the intended unblinding with the sponsor personnel. The occurrence of any emergency unblinding during the study must be clearly justified and explained by the investigator. In all cases, the sponsor personnel must be informed as soon as possible before or after the unblinding.

Once unblinding has occurred, the knowledge of the blinded treatment assignment must stay restricted at the site level.

A study participant may stay on study treatment after unblinding provided the investigator considers it is in the participant's best interest.

The circumstances leading to unblinding must be documented in the hospital charts, the ISF, and in the IRT system.

6.1.6 Study treatment handling/preparation/storage/accountability

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, GCP, and any local or national regulatory requirements.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

6.1.6.1 Study treatment packaging and labeling

Study treatment is provided as capsules and supplied in childproof bottles.

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

6.1.6.2 Study treatment distribution and storage at the site

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label and in the IB and/or Investigational Medicinal Product handling manual [ACT-539313 IB].

6.1.6.3 Study treatment dispensing

The study participants will receive sufficient study treatment to cover the period up to the next scheduled visit. Study participants are asked to return all used, partially used, and unused study treatment bottles at each visit. Should the treatment bottle dispensed at a scheduled visit be lost or damaged, a replacement bottle can be requested via the IRT system. In exceptional circumstances (e.g., pharmacist not available on the date of the scheduled visit), the investigator/delegate may contact the IRT system shortly prior to the scheduled visit (with the exception of the randomization visit [see Section 6.1.3] to obtain the treatment kit number(s) to be dispensed at the visit.

The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. In exceptional circumstances (e.g., if the study participant lost the study treatment between two visits, or if the study participant is unable to return to the site due to a medical emergency / hospitalization at another hospital / long travel distance), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. If the study treatment needs to be shipped to the study participant, the site staff must first contact the sponsor representative to check whether the dispensing and delivery process is in accordance with the sponsor/CRO's Quality System documents as well as any local or national regulatory requirements.

An accurate record of the date and amount of study treatment dispensed to each study participant must be available for inspection at any time.

Study participant will be dispensed new bottle(s) at each visit. Study drug from the newly received bottle is always to be taken in the evening at home.

The morning dose will be taken at home from the current bottle, except for Visit 5 (Week 4), Visit 7 (Week 8) and EOT visit where the morning dose will be withheld until the participant is on site and will be taken after PK laboratory samples are drawn.

6.1.6.4 Study treatment accountability

The inventory of study treatment dispensed to and returned by the study participant (i.e., study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. The inventory is to be recorded by site personnel in the site documentation and in the eCRF. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit dispensed to the study participant:

- Number of bottles dispensed
- Dispensed bottle ID number
- Date dispensed / number of capsules dispensed
- Date returned / number of capsules returned

All study treatment supplies, including partially used or empty bottles must be retained at the site until verified by the CRA.

If the study participant forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any capsules from the remaining study treatment bottle and to return it at the next visit.

6.1.6.5 Study treatment return and destruction

The protocol-mandated study treatment returning procedures may not be altered without prior written approval from the sponsor. On an ongoing basis and/or on termination of the study, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where the sponsor/depot personnel or a deputy will check treatment reconciliation.

In certain circumstances (e.g., local hospital procedures), used and unused study treatment containers may be destroyed at the site. In general, this can only be done once study treatment accountability is finalized and has been checked by the sponsor personnel representative and written permission for destruction has been obtained from the sponsor. Exception might happen in case a local process requests immediate destruction of the study treatment. Such local study treatment destruction processes must be provided and approved by the sponsor in advance.

6.1.7 Study treatment compliance

The investigator/delegate must discuss the non-compliance with the study participant to clarify the reasons and to take appropriate actions to avoid re-occurrence. This discussion and its outcome must be documented in the source documents.

6.2 Previous and concomitant medications

A previous medication / non-pharmacological therapy is any treatment for which the end date is prior to the start of study treatment.

A concomitant medication / non-pharmacological therapy is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

6.2.1 Allowed concomitant therapy

Therapies considered necessary for the study participant's well-being and not categorized as prohibited concomitant medications can be used in this study and must be documented in the medical charts. However, initiation of a new medication is to be discouraged and any concomitant (i.e., ongoing maintenance) medication will preferably not be changed during the study.

6.2.2 Forbidden concomitant therapy

Study participants must not be withdrawn from medically necessary therapies in order to participate in the study. These participants must rather be considered as non-eligible for the study due to their medical condition and their requirement for these therapies.

The following concomitant therapies are forbidden during the study:

- CNS-active drugs, such as centrally active anticholinergics, sedating antihistamines, morphine and other opioids, anticonvulsants, antidepressants, anxiolytics, mood

stabilizers, antipsychotics, stimulants, sleep drugs, and anti-Parkinson's drugs within 30 days prior to Screening or planned to be initiated during the study and until EOS.

- Medications that affect body weight or appetite, including weight-loss medications, insulin, GLP-1 receptor agonists, systemic corticosteroids etc., within 3 months prior to Screening and until EOT.
- Moderate and strong inducers and inhibitors of CPY3A4, sensitive substrates of CYP3A4, CYP2C19, CYP2C8, and CYP2C9 within 2 weeks prior to randomization (Visit 2) or planned to be initiated during the study and until 24 h after EOT.
- Any medications for the treatment of BE, including lisdexamfetamine (Vyvanse®), any other eating disorder, obesity, or weight gain, or any other medication that could result in weight gain or weight loss including over the counter and herbal products within 3 months prior to Screening.
- Psychotherapy or behavioral weight-loss interventions for BED during the study and until 24 h after EOT.

6.3 Medical care of study participants after study completion / withdrawal from study

After the study participant's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to study participants what treatment(s) / medical care is necessary and available according to local medical practice and applicable guidelines.

Female study participants of childbearing potential will be reminded of the contraception requirements as described in Section 5.5.2.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS AND PROCEDURES

7.1 General information

The treatment period starts with the administration of the first dose of study treatment and ends on the day of the last dose of study treatment (EOT). The study participants will be treated for 12 weeks.

The safety follow-up period **s**tarts on the day after the last dose of study treatment (EOT) and ends at the EOS visit.

For participants who prematurely discontinue study treatment, the EOT visit will occur within 5 days of the last intake of study treatment. For participants who complete the treatment period as planned, the Week 12 visit corresponds to the EOT visit.

The study visits and their respective time windows are listed in the schedule of activities [Table 1]. All assessments pertaining to a visit must be performed on the same day. If it is

not possible to complete all assessments on the same day, a visit may extend over more than 1 day within the allowed time window.

7.1.1 Screening

The study participants who agree to be part of the study and the investigator/delegate must sign the ICF prior to participation in the study. The ICF must be fully signed [see Section 10.2 for informed consent procedure] on the day of the Screening visit.

Screening starts with the signature of the ICF. The date on which the first screening assessment is performed corresponds to the date of the Screening visit. Screening assessments may be performed at any time during the screening period.

It is the responsibility of the investigator/delegate to obtain written informed consent from each participant in this study after adequate face-to-face explanation of the study objectives, design, and potential hazards of the study.

If the first study-specific procedures or assessments are performed on the day that the ICF is signed, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed (i.e., time of signature must be available).

Procedures or assessments conducted as part of the study participant's routine clinical management (e.g., laboratory samples) which were obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of activities [Table 1]. In such cases, it must be clear from the source documents when and for which reason the assessment was done prior to the signing of the ICF.

After the ICF has been fully signed, the investigator/delegate contacts the IRT system to get a study participant number allocated to the study participant.

It is not permitted to re-screen study participants in this study.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study and will be recorded in the eCRF. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the schedule of activities [Table 1].

7.1.3 Study completion

A study participant who completes 12 weeks of treatment and the safety follow-up period is considered to have completed the study per protocol. A study participant who

prematurely discontinues the study due to pre-defined criteria [see Section 5.9.1], withdrew from the study, was lost to follow-up, or was withdrawn from the study because of study closure or premature termination or suspension of the study [see Section 10.10] is considered as an early discontinuation.

7.2 Study assessments and procedures

The study assessments and procedures and their timing are summarized in the schedule of activities [Table 1].

All study assessments performed during study visits (scheduled or unscheduled) are done by the investigator/delegate and are recorded in the eCRF, unless otherwise specified.

In general, it is recommended to start visits by performing blood sample collection, so that study participants do not stay under fasted conditions too long. Questionnaires and scales are *recommended* to be performed in the following order:

At Screening:

- SCID-5 (paper-based) to confirm diagnosis of BED
- EDE-Q (ePRO) which helps confirm diagnosis of BED and rule out bulimia nervosa
- MINI (paper-based) should ideally be done after the EDE-Q
- CGI-S (ePRO), taking into account results of all other eating disorder evaluations
- Instructions to the study participant on how to complete the BE diary (paper-based)

At Randomization and subsequent visits:

- Review of paper-based questionnaires BE diary (and SSS)
- YBOCS-BE (ePRO)
- CGI-S (ePRO)
- Other scales can be done in order of investigator's clinical judgment

[redacted]

The following assessments will be analyzed by an external provider (results will be transferred to sponsor and to the investigators):

- Laboratory variables

- ECG variables
- Questionnaires completed using a touchscreen device (handheld tablet device or laptop), listed below.

If the PI delegates any study procedure/assessment for a study participant to an external facility, he/she must inform the sponsor to whom these tasks are delegated. The setup and oversight must be agreed upon with the sponsor. The supervision of any external facilities remains the responsibility of the PI.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the recruitment of the first study participant. Calibration certificates / evidence of equipment maintenance for other equipment must be available as per local requirements.

Equipment for which calibration certificates are needed:

- Temperature measurement devices for study treatment storage area and laboratory sample storage (e.g., freezer)
- Body-weight scale
- Use of touchscreen device
- Study participants will be required to complete the following questionnaires on a touchscreen device at the study site/clinic during the appropriate visit days [see Table 1 and Sections 7.2.3 and 7.2.4 for further description of the respective questionnaires]:
- EDE-Q, BWSQ, PGI-S, PGI-C, [redacted] tasks
- Investigators, delegated physicians, specialist nurses or nurse practitioners trained according to local requirements and local clinical practice will be required to complete the following questionnaires on a touchscreen device at the site:
  - YBOCS-BE, HAMD-17, C-SSRS©, CGI-S, CGI-C
- Sites will be properly trained on the accurate use of the touchscreen device by the sponsor or an external CRO and are then expected to train their study participants on how to appropriately complete the questionnaires. Data collected from the touchscreen device will be electronically transferred to the sponsor by the CRO.
- For further details refer to the touchscreen device manual.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristics data to be collected in the eCRF for all study participants include: age, sex, race and ethnicity (if allowed in the country). Relevant medical history and/or current medical conditions, based on the investigator/delegate's judgment (e.g., chronic and ongoing acute conditions, serious past conditions including

previous surgeries), present before and/or at the time of signing of the ICF will be recorded in the eCRF. Where possible, diagnoses rather than symptoms will be recorded.

The reason for not being of childbearing potential will be recorded in the eCRF.

7.2.2 Reporting of previous/concomitant medications / non-pharmacological therapy / medical or surgical interventions or procedures and methods of birth control in the eCRF

A concomitant medication / non-pharmacological therapy is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

A previous medication / non-pharmacological therapy is any treatment for which the end date is prior to the start of study treatment.

The use of all concomitant medications / non-pharmacological therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous medications / non-pharmacological therapy must be recorded in the eCRF if discontinued less than 30 days prior to signing of the informed consent.

Any medical or surgical intervention performed on the study participant at any time during the study, will be documented in the eCRF.

The methods of birth control used (including non-pharmacological methods) by the WOCBP (and partner if applicable) must be recorded in the eCRF.

In addition, the investigator/delegate will record any change in the method of contraception in the eCRF at monthly intervals and will remind the study participant to follow the protocol-mandated method of contraception up to 30 days after study treatment discontinuation.

Note: The documentation of method of contraception can be based on the site personnel's review of the study participant's medical records, medical examination, or medical history interview of the study participant.

7.2.3 Eligibility assessments

7.2.3.1 Structured Clinical Interview for DSM-5 - Clinical Trial Version (SCID-5)

The SCID-5 is a semi-structured interview guide for making the major DSM-5 diagnoses. It is conducted by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria.

The SCID-5 Eating Disorder module will be conducted at Screening to diagnose BED and to exclude other eating disorders e.g., anorexia nervosa and bulimia nervosa.

7.2.3.2 Eating Disorder Examination Questionnaire (EDE-Q)

The EDE-Q is a 28-item scale that assesses attitudinal and behavioral dimensions of the eating psychopathology in BED. It will be used to confirm the SCID-5 diagnosis of BED. EDE-Q focuses on the previous 28 days, except for the diagnostic items that are rated for the durations stipulated in the DSM-5 (SCID-5).The EDE-Q also assesses in more detail the frequency of different forms of overeating, including objective bulimic episodes (binge eating defined as unusually large quantities of food with a subjective sense of loss of control) and subjective bulimic episodes (defined as a subjective sense of loss of control but a normal or small amount of food).

The EDE-Q will be answered by the study participant and reviewed by a clinician or trained mental health professional to confirm the diagnosis of BED as well as to confirm the self-reported severity of binge eating in BE days, based on the last 28 days. The full EDE-Q (28-item) version will be assessed at Visit 1.

7.2.3.3 Mini International Neuropsychiatric Interview©

The MINI© is a psychiatric examination [Sheehan 1999] used to identify study participants with exclusionary psychiatric conditions. The MINI© will be conducted at Screening by a trained clinician. The MINI© will be conducted to ascertain the psychiatric diagnoses, and any clinically relevant psychiatric conditions will be reported in the eCRF.

7.2.3.4 Binge Eating Diary

The number of BE episodes will be recorded by the study participant daily, preferably in the evening, for at least 2 weeks prior to randomization in a paper-based diary. The diary captures the number of binges per day, total time spent BE each day, type of binge (mealtime vs non-mealtime), and a description of the binge (amount and types of food). A BE day is defined as a day with at least one BE episode. These data will be reviewed by the investigator with the study participant at Visit 2 and will determine whether the participant meets inclusion criterion 9. The investigator will confirm whether each recorded eating episode is a binge or not. The number of confirmed binges each day will also be recorded in the eCRF.

7.2.4 Efficacy assessments

The schedule of activities is presented in Table 1.

7.2.4.1 Binge Eating Diary

As above, the number of BE episodes will continue to be recorded by the study participant daily, preferably in the evening, until end of study treatment. Data from the diary will be reviewed by the investigator with the study participant at each visit until end of study treatment and will help the investigator confirm whether each recorded eating episode is a

binge or not. The number of confirmed binges each day must be recorded in the eCRF. A BE day is defined as a day with at least one BE episode.

7.2.4.2 Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating

The YBOCS [Goodman 1989] is an interviewer-administered assessment developed to measure the severity of obsessive-compulsive symptoms in patients with a diagnosis of OCD. The YBOCS-BE is a version of the YBOCS modified to measure the obsessiveness of BE thoughts and the compulsiveness of BE behaviors. The BE behavior of BED is similar to an OCD compulsion in that it is time-consuming, distressing, may inhibit or hinder functioning, and may or may not be successfully resisted [Deal 2015]. The scale has been modified by replacing the term "obsessive thoughts" with "thoughts, impulses, or ideas to binge eat" for the first 5 items, and "compulsive behaviors" with "binge eating" for items 6–10. The 10 items are clinician/investigator-rated on a 5-point Likert scale. The YBOCS-BE [Machado 2020,Yee 2019] will be administered on a touchscreen device on site, at Visit 2 (Randomization), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.3 Clinical Global Impression of Severity Scale

The CGI-S is a 1-item, 7-point scale that requires the investigator to rate the severity of the study participant's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis.

After a clinical evaluation, the CGI-S form can be completed in less than a minute by an experienced rater. In practice, the CGI-S captures clinical impressions that transcend mere symptom checklists. It ranges between "Normal, not at all ill" and "Among the most extremely ill patients". The CGI-S will be administered on a touchscreen device on site, at Visit 1 (Screening), Visit 2 (Randomization), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.4 Clinical Global Impression of Change Scale

The CGI-C is a 1-item, 7-point scale that requires the clinician to assess how much the study participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The range is between "Very much improved" and "Very much worse". The CGI-C will be administered on a touchscreen device on site at Visit 3 (Week 1), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.5 Patient Global Impression of Severity scale

The PGI-S is a question concerning the overall severity of symptoms and impact that the study participant may have experienced due to his/her BE episodes over the 7 days preceding the PGI-S completion.

It ranges between "No binge eating" and "Very severe". It is a self-administered questionnaire completed on a touchscreen device on site at Visit 2 (Randomization), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.6 Patient Global Impression of Change scale

The PGI-C is a 1-item, 7-point scale that asks the study participant to evaluate all aspects of his/her health and to assess if there has been an improvement or decline in clinical status from the baseline of the observation.

The scale starts at "Very much worse" escalating to "Very much improved". The PGI-C will be administered on a touchscreen device on site at Visit 3 (Week 1), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.7 Eating Disorder Examination Questionnaire (EDE-Q7)

The EDE-Q7 is a self-reported questionnaire containing 7 out of the 28 questions from the EDE-Q about eating behaviors (Items #1, 3, 4, 22, 23, 25 and 26). It will be completed on a touchscreen device on site at Visit 2 (Randomization), Visit 5 (Week 4), Visit 7 (Week 8), and EOT (Week 12).

7.2.4.8 Hamilton Depression Rating Scale (HAMD-17)

The HAMD-17 [Hamilton 1960] will be used to provide an indication of depression. The total score will be used to exclude study participants with symptoms of depression of at least moderate severity at baseline (score of 17 or more). In addition, it will also be used to assess the change from baseline to Weeks 6 and 12 on the total score in study participants who may have signs of depressive symptoms as well as on its anxiety-related subitems 10 & 11 and the MPS. The MPS combines the items 1, 2, 7, 8, 9, and 10 and is an observational rating measure to assess the severity of depressive symptoms and its improvement under therapy. It will be completed on a touchscreen device on site at Visit 1 (Screening), Visit 2 (Randomization), Visit 6 (Week 6), EOT (Week 12), and EOS.

[redacted]

[redacted]

7.2.4.10 Body weight and height

Body weight will be measured at all visits up to EOT and recorded in the eCRF. Height will only be measured at Screening. Body weight measurements will be done in lightweight clothes, without shoes, with an empty bladder, and approximately at the same time of the day. The same calibrated scale should be used throughout the trial.

The BMI will be calculated at Visit 1 (for eligibility) and displayed automatically upon entry of weight and height in the eCRF.

Unless otherwise specified, the date of each assessment will be collected in the eCRF.

7.2.5 Safety assessments

Unless otherwise specified, the date of each assessment will be collected in the eCRF.

The definitions, reporting, and follow-up of AEs, SAEs and pregnancies are described in Section 8.

7.2.5.1 Physical examination

Physical examination includes the examination of the general appearance (heart, lungs, abdomen, skin, extremities, eyes, ears, nose, throat, lymph nodes, nervous system, etc.). Physical examination is to be performed at Visit 1 and at EOT visit.

Other examinations will be performed if indicated, based on medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site.

The physical examination will be reported in the eCRF as either normal or abnormal; in the latter case, the investigator should specify whether it is clinically relevant. Clinically relevant findings (other than those related to BED) that are present prior to signing the ICF must be recorded as medical history in the eCRF. Physical examination findings, which meet the definition of an AE [Section 8.1.1] and are made after signing of the ICF, must be recorded on the AE form of the eCRF.

7.2.5.2 Vital signs

Oral or axillary temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic) will be assessed and recorded in the eCRF. The date and actual time of vital sign measurements will be entered in the eCRF. Any clinically significant abnormal vital sign

value should be repeated after a reasonable interval (e.g., 10–15 min) to ensure accuracy. If the abnormality persists upon repeat measurement, the participant should be assessed by the investigator.

Blood pressure and pulse measurements will be assessed with the study participant in a seated position. It is recommended to allow the study participant to rest for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones), and to use the same position (i.e., sitting), same device and same arm throughout the study for an individual study participant.

Vital signs are to be assessed at each visit until EOT visit.

7.2.5.3 Electrocardiograms

A standard 12-lead ECG will be performed at Visit 1 (Screening) and EOT visit using the ECG machine provided by the central ECG vendor. ECGs will be performed with the study participant in a fully rested supine position after the study participant has been allowed to rest for a minimum of 5 minutes. The date and actual time of ECGs will be recorded in the eCRF.

A central ECG vendor (see ECG manual for contact details) will be used for the evaluation of all protocol-mandated ECGs, including re-tests due to ECG abnormalities and ECGs performed at unscheduled visits. The site personnel will electronically transmit the ECGs to the central ECG vendor for central reading.

The 12-lead ECG measurements (e.g., HR and the intervals PR, QRS, QT, QTcF, and QTcB), qualitative ECG findings (e.g., rhythm, ectopy, conduction and morphology) and the overall interpretation of the ECG (normal/abnormal) will be provided by the ECG central vendor.

ECG reports will be provided by the central ECG vendor to the investigator/delegate. If specific (pre-defined in the ECG manual) ECG abnormalities are observed, the central ECG vendor will alert the sponsor and the investigator/delegate.

All ECG reports must be reviewed, signed and dated by the investigator or delegate within 10 calendar days of receipt and filed with the source documentation. The investigator/delegate must indicate on the ECG report whether abnormal values or findings are considered clinically relevant or not. Clinically relevant ECG findings that are known at the time of signing of the ICF must be recorded as medical history in the eCRF.

Details on ECG procedures (recording, transfer of data and reporting) will be provided in the ECG manual.

7.2.5.4 Clinical laboratory assessments

See schedule of activities [Table 1] for the timing and frequency.

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Exceptional circumstances that may require recording of local laboratory results (with corresponding normal ranges) include hospitalization of the study participant due to a medical emergency and missing central laboratory results from a scheduled or unscheduled visit.

If two or more consecutive central laboratory samples are lost or cannot be analyzed for whatever reason, the investigator/delegate will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time window and these test results are available.

Under specific circumstances (e.g., if the study participant lives far from the site and cannot return every month), laboratory samples may be collected at a laboratory close to where the study participant lives (satellite laboratory) and sent to the central laboratory for analysis. In such a case, the satellite laboratory must be provided with the central laboratory sampling kits. Shipment of the samples will be organized by the satellite laboratory. The supervision of the satellite laboratory remains the responsibility of the PI.

Central laboratory reports will be sent to the investigator. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert the sponsor personnel and the concerned site personnel. Alert flags that will trigger such notifications will be displayed in the laboratory manual.

All laboratory reports must be printed, reviewed, signed and dated by the investigator or delegate within 5 calendar days, and filed with the hospital chart. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically relevant or not. Clinically relevant laboratory findings that are known at the time of signing of the ICF must be recorded as medical history in the eCRF.

Blood samples will be drawn in the morning under fasted conditions (i.e., before breakfast) and when applicable before the morning administration of the study treatment at all scheduled and unscheduled visits. However, it is not permitted to request that study participants are in a fasted state (for the study) at the Screening visit unless the ICF has already been signed.

A serum pregnancy test for WOCBP will be performed at the Screening visit and EOT visit.

Urine pregnancy tests will be performed at randomization before first study treatment administration (Visit 2) and monthly thereafter (i.e., Visit 5 and Visit 7) up to EOS visit. Urine pregnancy tests will be performed with locally approved kits.

The results of the urine pregnancy tests will be collected in the eCRF. Serum pregnancy tests will be sent to the central laboratory for analysis and the result will be sent to the investigator/delegate. If pregnancy is suspected during the study, i.e., in each case of delayed menstrual period (e.g., over one month between menstruations), a serum pregnancy test must be performed as soon as possible. Reporting procedures of pregnancy are described in Section 8.3.1.

Hematology:

- Hemoglobin
- Hematocrit
- Erythrocytes
- Reticulocyte
- Leukocytes with differential counts
- Platelets.

Clinical chemistry:

- ALT
- AST
- Alkaline phosphatase
- Creatine kinase
- Total and direct bilirubin
- Gamma-glutamyl transferase
- Creatinine and estimated glomerular filtration rate
- Blood urea nitrogen
- Uric acid
- Glucose
- HbA1c
- Total cholesterol
- Triglycerides
- Sodium, potassium, chloride, calcium
- Albumin
- Thyroid hormones, i.e., triiodothyronine (total and free) and thyroxine (total and free), and TSH (Visit 1 only).

Viral serology:

- At Screening, blood sample will be collected to test for HIV, Hepatis B and C.

Other tests:

The urine drug screening kits (testing for presence of benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine or cocaine) will be provided by the central laboratory.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.5.5 Stanford Sleepiness Scale

The SSS [Hoddes 1972, Hoddes 1973] is a self-administered questionnaire that uses a 7-point Likert scale, developed to quantify the subjective sleepiness at any given time. Participants will be asked to pick the response (number) that best represents how they are feeling two times during the day: once before breakfast (i.e., before the morning dose of the study treatment) and then at midday or any time before lunch to capture daytime sleepiness temporally related to intake of study treatment. Participants will be asked to answer the paper based SSS questionnaire during the first 2 weeks after randomization. This will then be transcribed by the site into the eCRF.

7.2.5.6 Benzodiazepine Withdrawal Symptom Questionnaire

The BWSQ assesses the occurrence of symptoms which might be experienced by study participants after discontinuation of treatment with ACT-539313 [Tyrer 1990]. The questionnaire consists of 20 items. The symptoms will be rated from 0 (No), 1 (Yes-moderate) to 2 (Yes-severe). The questionnaire will be self-administered using the touchscreen device at EOT visit and EOS visit.

7.2.5.7 Columbia Suicide Severity Rating Scale©

The C-SSRS© is an instrument that reports the presence and severity of both suicidal ideation and behaviors.

Suicidal ideation is classified on a 5-item scale:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (no plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

The C-SSRS© also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation.

In addition, the C-SSRS© captures information using yes/no questions and answers on suicidal behaviors, specifically: actual, interrupted, and aborted attempts; preparatory acts

or behaviors; and the presence of suicidal behaviors during the assessment period. More than one classification can be selected, provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

At Screening the C-SSRS© will be completed for the study participant's lifetime history of suicidal ideation and behaviors and participants who answer "yes" *in the past month* to items 2, 3, 4, or 5 on the C-SSRS© assessment will be excluded from the study [see Section 5.4, criterion #26). At all other visits, the C-SSRS© will be completed for ideation and behaviors since the previous visit. All time points will be collected on a touchscreen device on site.

Participants who answer "yes" to items 2, 3, 4, or 5 on the C-SSRS© assessment at any post-randomization visit must undergo further evaluation by the investigator to assess the risk. No study treatment will be dispensed to such participants until after the investigator confirms suitability of the participant to remain in the study. This evaluation and decision should also be clearly recorded in the source documents.

As part of routine clinical care, participants will be provided with 24-hour emergency contact details in the event of an emergency should the participant feel that he/she is acutely at risk. In addition, participants who are recruited into the study will be advised of the location of their nearest hospital.

7.2.5.8 Assessments in the context of COVID-19: Recommendations and instructions

Flexibility regarding site visits for study participants who can still go to sites

If the study participant can travel to the investigator's site:

- The investigator should ensure the study participant's safety on his/her way to the site by following local/country regulations (e.g., not using public transportation). Alternatively, study participants can use taxis or private cars, the cost of which will be reimbursed by the sponsor.
- The on-site visit assessments should be performed according to the protocol.
- An on-site visit is always preferable. Therefore, this may mean that the visit windows need to be extended, as long as the study participant has enough study treatment. Study treatment can be delivered to the study participant's home following the instructions below. The reason for this delayed scheduled visit must be documented in the study participant's medical charts and in the eCRF.

Conduct of remote visits for study participants who cannot, are not allowed to, or are not willing to travel to the investigator's site

If the study participant cannot, is not allowed to, or is not willing to travel to the investigator's site, the clinic visit(s) can be replaced by a telephone call or video call to keep close contact with study participants (remote visits), these visits should be at least as frequent as the protocol-mandated clinic visits. The investigator should notify the IEC / IRB in advance of remote visits if this is a local requirement.

Before the telephone call or video call visit:

If the study treatment needs to be delivered to the study participant's home, the investigator should ensure the following:

- Obtain study participant's verbal consent by telephone to provide his/her name and home address to the courier service responsible for delivering study treatment and pregnancy tests, if applicable.
- The date and time that verbal consent was obtained is documented in the study participant's medical records.
- Make sure that WOCBP have enough home urine pregnancy kits (send them along with study medications to the study participant's home if necessary) and remind them to perform the test as mandated by the protocol.
- If the approval must be in writing, according to the site's local regulation, the investigator/delegate must act accordingly and document it in the study participant's medical charts.
- Arrange for the delivery of study treatment (in accordance with local regulation) to the study participant's home in advance.
- Arrange for the delivery of additional BE diaries and SSS questionnaires.
- Arrange for the delivery of appropriately calibrated devices for measuring vital signs to the study participant's home in advance. Clear instructions on how to use these devices will also be provided on paper; in addition, the investigator or site staff will review these instructions with the participant.

During the telephone call or video call visit:

All efforts should be made to collect the same information as collected during an on-site visit. The investigator will check and record the vital signs measured by the participant using the devices provided. Efficacy data will be collected, questionnaires and other assessments should be performed, even remotely, if possible. To ensure study participants' safety, investigator/delegate will conduct an interview to detect any potential AE as described below.

Special attention is to be paid to the primary efficacy endpoint. Each study participant will go over the BE diary entries with the investigator who will confirm whether each recorded eating episode is a binge or not.

The investigator will interview the study participant for:

- Occurrence of any new AEs or worsening of existing ones.
- When asking about the occurrence of AEs, please follow the same process as for a site visit, i.e., use an open-ended question, such as: "Have you had any significant medical problems since the last study visit?".
- Collection of additional information about AESI as applicable.
- Reviewing the SSS entries with the study participant to check for daytime sleepiness symptoms (Visit 2, Visit 3 and Visit 4 only).
- Assessing withdrawal symptoms (only applicable between EOT and EOS visits).
- Completion of the C-SSRS© questionnaire, on-site by the investigator.
- Completion of the YBOCS-BE, on-site by the investigator.
- Completion of the HAMD-17, on-site by the investigator.
- Completion of the CGI-S and CGI-C, on-site by the investigator.
- Reviewing SSS scores (in addition to BE diary data). These paper-based questionnaires, completed at home by study participant, will have to be brought back to the site at the next visit.
- Changes in any ongoing medication or start of new medication(s).
- Check compliance with study medication and potential overdose or other medication error(s).

Note: If closer monitoring of any of the above detected findings is required but not possible, depending on the severity of the symptoms observed and the investigator's assessment of the benefit-risk for the study participants inclusion in the trial, the investigator may consider discontinuing treatment while trying to maintain the study participant in the study.

The telephone or video contact must be entered under the visit it replaces (e.g., if the assessments were intended for Visit 3, please use the Visit 3 form) and documented in detail (day, time and conversation) in the study participant's medical charts. All assessments not performed must be entered as "Not done".

Should any additional telephone calls be performed to ensure the study participant's safety that are not part of the regular visit plan, the call must be entered as an unscheduled visit in the eCRF and documented in detail (day and reason for the 'UNS') in the study participant's medical charts.

7.2.5.9 COVID-19 testing

There is no mandatory COVID-19 testing required as part of this protocol. Testing for SARS-Cov-2 virus will be done as per each site's local requirements. The need to perform COVID-19 testing for a study participant already enrolled in the study will likewise be guided by the site's local standard measures and requirements. See Section 5.9.1.4 for details on what happens to a study participant who becomes infected during the study.

7.2.6 Pharmacokinetic assessments

PK samples will be collected prior to the morning dose at Visit 5 (Week 4), Visit 7 (Week 8), and EOT visit (Week 12). The date and the time of blood sample collection will be entered in the eCRF. The date and time of the last study treatment dosing before blood draw will also be entered in the eCRF.

Details about the collection, sampling, storage, and shipment procedures can be found in the laboratory manual.

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Safety definitions

8.1.1 Definition of adverse events

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a study participant during the course of the study, whether or not considered by the investigator/delegate as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease if considered medically relevant.
- Exacerbation of a pre-existing disease with the exception of efficacy endpoints and associated symptoms.

- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen after the signing of the ICF.
- Abnormal change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study as per investigator medical assessment.
- Laboratory test abnormalities if they represent a clinically significant finding (symptomatic or not) which was not present at study start or worsened during the course of the study as per investigator judgment, led to dose reduction, interruption or permanent discontinuation of study treatment.

8.1.2 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization (i.e., the AE required admission to hospital) or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs based upon appropriate medical judgment, as they may jeopardize the study participant, and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing the ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a study participant with stable angina pectoris.

8.1.3 Intensity of adverse events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- **Mild**

The event may be noticeable to the study participant. It does not usually influence daily activities, and normally does not require intervention.

- **Moderate**

The event may make the study participant uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- **Severe**

The event may cause noticeable discomfort and usually interferes with daily activities. The study participant may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

8.1.4 Relationship to study treatment

Each AE/SAE must be assessed by the investigator/delegate as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated.

8.1.5 Relationship to study design or protocol-mandated procedure

An AE/SAE is defined as related to the study design or protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure.

The determination of the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator/delegate.

8.1.6 Definition of adverse events of special interest

AESIs for this study include AEs related to somnolence, defined by pre-specified terms. At each visit, as per good clinical care, the investigator must ask the study participant for any AEs and specifically ask for the occurrence of somnolence and document this as appropriate.

8.1.7 Definition of study treatment overdose, misuse and abuse

An overdose is defined as the administration of a study treatment dose (per intake or cumulatively) which is above the instructions provided in the protocol. When applying this definition, clinical judgement should always be applied.

The sponsor does not recommend specific treatment for an overdose.

Study treatment misuse is defined as any **intentional and inappropriate use** of the study treatment which is different from the instruction provided in the protocol.

Study treatment abuse is defined as any **intentional and excessive use** of the study treatment with harmful physical or psychological effects.

In the event of a study treatment overdose, abuse or misuse, the investigator/delegate must contact the sponsor and closely monitor the study participant for any AEs/SAEs.

If a mismatch is detected during study medication compliance check, the investigator should review and record in the eCRF as an AE if it is consistent with a medication error or overdose. The number of extra capsules taken, the time period, and whether it was intentional or accidental must also be recorded in the eCRF.

8.2 Reporting procedures

8.2.1 Reporting and follow-up of AEs

The occurrence of an AE may come to the attention of study personnel during study visits, telephone calls, or interviews of study participants presenting for medical care.

At each study visit (scheduled or unscheduled), the investigator/delegate will inquire about the occurrence of AEs since the last visit.

All AEs with an onset date after signing of the ICF up to EOS must be recorded in the eCRF.

The AE should be reported as a final diagnosis (if possible) rather than a list of symptoms.

Information to be collected on an AE form in the eCRF includes date of onset, time of onset, action taken with the study treatment, outcome of the AE, date and time of resolution (if applicable), and PI/delegate's assessment of intensity as well as its relationship to study treatment or protocol-mandated procedures.

Information on worsening of intensity will be collected. If the AE lessens in intensity, no change in the severity is required to be reported.

AEs still ongoing after study treatment discontinuation must be followed up until resolution, until they are no longer considered clinically relevant, or until stabilization.

8.2.2 Reporting and follow-up of SAEs

All SAEs must be reported by the investigator/delegate to the sponsor's Global Drug Safety department within 24 hours of site staff's first awareness/knowledge of the event.

All SAEs occurring after signing of the ICF up to EOS must be recorded on an SAE form, regardless of the investigator/delegate-attributed causal relationship with study treatment or study-mandated procedures.

The SAE forms must be sent to the sponsor's Global Drug Safety department (see contact details on the SAE form). The investigator/delegate must complete the SAE form in English and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must be promptly reported. The sponsor's Global Drug Safety personnel may contact the investigator/delegate to obtain further information.

If the study participant is hospitalized in a hospital other than that of the study site, it is the investigator/delegate's responsibility to contact this hospital to obtain all SAE-relevant information and documentation.

New SAEs occurring after EOS must be reported to the sponsor's Global Drug Safety department within 24 hours of site staff's first awareness/knowledge of the event**, only** if considered relevant and study treatment-related by the investigator/delegate.

SAEs still ongoing after EOS must be followed up until resolution, stabilization, or until the event outcome is provided.

8.2.3 Reporting procedure for SUSARs

The expectedness of an SAE is determined by the sponsor according to the reference safety information section provided in the IB.

Any SAE that is assessed as related and unexpected against the reference safety information is considered as a SUSAR.

Any SUSAR must be reported by the sponsor or designee (CRO) as determined to concerned health authorities, and investigators. Submission to central/local IECs/IRBs will be done as per their requirements.

8.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued [see Section 5.9.1.1]. The investigator/delegate must counsel the study

participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

8.3.1 Reporting of pregnancy

Any pregnancy occurring in a female study participant after signing of the ICF and up to EOS must be reported to the sponsor's Global Drug Safety department within 24 hours of site staff first awareness/knowledge of the event.

All pregnancies must be reported on the sponsor Pregnancy form, which is sent to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form).

The investigator must complete the Pregnancy form in English.

8.3.2 Follow-up of pregnancy

Any pregnancies must be followed up to their conclusion and the outcome must be reported to the sponsor's Global Drug Safety department.

Any AE associated with the pregnancy of a female study participant occurring during the AE reporting time must be reported on separate AE forms in the eCRF as described in Section 8.2.1.

Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 8.2.2.

9 STATISTICAL METHODS

All statistical analyses will be conducted by the sponsor or by a designated CRO supervised by the sponsor.

A SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

9.1 Analysis sets

9.1.1 Screened set

The SCR includes all study participants who entered screening and have a study participant identification number.

Summaries based on the SCR set will be presented as one group (i.e., all study participants).

9.1.2 All randomized set

The All-randomized analysis set includes all study participants from the SCR who were randomized.

9.1.3 Full analysis set

The FAS includes all study participants who were randomized, received at least one dose of study treatment and have a baseline assessment of the primary endpoint.

In order to adhere to the intention-to-treat principle, study participants will be evaluated according to their assigned study treatment.

This set will be used for the analysis of the study participant demographics and disease baseline characteristics, and efficacy.

9.1.4 Per-protocol analysis set

The PPS includes all study participants from the FAS without protocol deviations that potentially affect the primary endpoint. These deviations will be defined in the SAP. Study participants will be evaluated according to the study treatment they received.

This set will be used for supportive analyses of the efficacy.

9.1.5 Safety set

The SAF includes all randomized study participants who received at least one dose of study treatment. Study participants will be evaluated according to the study treatment they received.

This set will be used for the analyses of exposure, previous and concomitant medication and safety data.

9.1.6 PK set

The PK analysis set includes all study participants in the SAF who have at least one PK sample collected after initiation of study drug.

9.1.7 Usage of the analysis sets

The main efficacy analyses will be performed on the FAS, and a supportive analysis will be conducted using the PPS.

Safety analyses will be performed on the SAF based on actual study treatment received.

Subject listings will be based on the SAF, unless otherwise specified. Subject disposition will be described for the SCR.

Table 3 describes the analysis sets used for the analysis of each data set.

Table 3 Usage of analysis datasets

Analysis	SCR	RND	FAS	PPS	SAF	PK set
Subject disposition	X					
Baseline demographics and disease characteristics	X	(x)	X	(x)		
Previous and concomitant medication					X	
Study drug exposure				(x)	X	
Efficacy analysis			X	x		
Safety and tolerability analyses					X	
PK data analysis						X

Note: X: main analysis, (x): only if > 10% difference in size with FAS.
FAS = Full analysis set; PK = pharmacokinetic; PPS = Per-protocol analysis set; RND = Randomized analysis set; SAF = Safety analysis set; SCR = Screened analysis set.

9.2 Description of statistical analyses

9.2.1 Overall testing strategy

The H_0 to be tested is that there is no difference between ACT-539313 and placebo with respect to the primary efficacy endpoint:

$$H_0: \mu_A = \mu_P \quad \text{vs} \quad H_a\ \mu_A \neq \mu_P$$

Here, μ_A and μ_P is the mean change from baseline to Week 12 in the number of BE days per week in the ACT-539313 and placebo group, respectively. The null hypothesis will be tested at a two-sided 0.05 significance level.

A preview of the main analyses is given in Table 4 using the estimand terminology [ICH 2020]. Estimands are defined by five attributes: treatment condition of interest, target population, endpoint, strategy for addressing intercurrent events (i.e., premature discontinuation of treatment or use of other, forbidden, medication for BE) and population-level summary. The primary estimand is based on the primary endpoint. A supplementary estimand is obtained by changing one or more attributes. For both estimands the treatment condition is ACT-539313 b.i.d. for up to 12 weeks, whereas the alternative condition is placebo b.i.d. for the same period. The other four attributes are given in the table below. Differences vs the primary estimand are indicated in ***bold italics***.

Table 4 Estimands for the primary objective

Estimand	Target Population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary Estimand	Adult study participants with BED according to DSM-5, having at least 3 BE days per week.	Change from baseline to Week 12 in the number of BE days per week.	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline (ACT-539313 minus placebo; from mixed model).
Supplementary Estimand #1	Adult study participants with BED according to DSM-5, having at least 3 BE days per week.	Change from baseline to Week 12 in the number of BE ***episodes*** per week.	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline (ACT-539313 minus placebo; from mixed model).
Supplementary Estimand #2	Adult study participants with BED according to DSM-5, having at least 3 BE days per week, ***completing 12 weeks of treatment without use of other medication.***	Change from baseline to Week 12 in the number of BE days per week.	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline (ACT-539313 minus placebo; from mixed model).

Intercurrent events are premature discontinuation of treatment and use of other, forbidden, medication for BE.
BE = binge eating; BED = binge eating disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (5th edition); LSMean = least squares mean.

9.2.2 Analysis of the primary efficacy outcome(s)

The main efficacy analyses will be performed on the FAS. Supportive analyses will be performed on the PPS.

9.2.2.1 Variable definition

The primary efficacy variable is the change from baseline to Week 11–12 in the number of BE days per week based on diary data. In the analysis, changes from baseline to intermediate time points will also be considered.

The number of BE days per week will be calculated based on 2-week (rather than 1-week) intervals in order to improve the precision of the variable. A minimum of 7 diary entries per 14-day time interval is required, otherwise the number of BE days will be considered missing.

The baseline number of BE days per week is defined as the number of diary days with at least one BE episode divided by the total number of diary days during the 14 days prior to randomization (study Days –14 to –1), times 7. A diary day is a day for which the number of BE episodes is entered in the study participant's diary (this includes a zero value, i.e., no BE episode).

The number of BE days per week at Weeks 1–2, 3–4, 5–6, 7–8, 9–10, and 11–12 are calculated similarly based on diary entries during study days 1–14, 15–28, 29–42, 43–56, 57–70, and 71–84, respectively.

9.2.2.2 Primary analysis

The primary analysis will be performed on the FAS. Measurements obtained after premature treatment discontinuation will be excluded from the analysis, leading to a hypothetical strategy estimand [the primary estimand, Table 4]. This estimand addresses the full potential of ACT-539313 which is most relevant for this type of study.

Changes from baseline to post-baseline time points in the number of BE days per week will be analyzed using a mixed model for repeated measurements with factors for treatment group, sex, BMI category (< 30 vs ≥ 30 kg/m^2) and time point (Weeks 1–2, 3–4, 5–6, 7–8, 9–10, and 11–12), treatment by time interaction and covariates for baseline number of BE days per week and the interaction between baseline and time point.

An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same study participant. If this analysis fails to converge, the following structures will be tested in a subsequent order until model-convergence is achieved: heterogeneous Toeplitz; Toeplitz; autoregressive; compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

A restricted maximum likelihood approach in combination with the Newton Raphson Algorithm will be used.

LSMeans for each treatment group and time point will be obtained from the mixed model. The null hypothesis associated with the primary endpoint is that there is no difference between ACT-539313 and placebo in the mean change from baseline to Week 11–12 in the number of BE days per week. This hypothesis will be tested at a two-sided significance level of 5% based on the (ACT-539313 minus placebo) difference in LSMeans at Weeks 11–12. The null hypothesis will be rejected if the 95% CI around this difference excludes zero.

Mean changes from baseline in the number of BE days per week by treatment group will be displayed graphically to illustrate the time course of the primary endpoint.

9.2.2.3 Handling of missing data and intercurrent events

All efforts will be implemented to minimize the amount of missing data. Visits are performed at regular and short intervals for the investigator to closely follow-up with the diary completion.

The primary efficacy analysis assumes a missing at random mechanism (i.e., missingness is conditionally independent from the unobserved values of the primary endpoint, given the covariates in the mixed model).

Potential impact of COVID-19 pandemic on statistical analyses. The COVID-19 pandemic may lead to missed or postponed visits, but the study participant's binge eating diaries can still be evaluated at the next visit to collect the information for the primary endpoint [see Section 7.2.5.8]. Any missing diary data due to the COVID-19 pandemic is considered missing completely at random and satisfies the assumption underlying the main analysis (linear mixed-effects model, assuming missing at random).

9.2.2.4 Sensitivity analyses

Sensitivity analyses will be performed assuming a missing not at random mechanism, where missingness is related to the unobserved value of the endpoint. The model will utilize a multiple imputations approach based on a control-based imputation, which assumes that missing values of study participants in the ACT-539313 group are similar to observed values of study participants in the placebo group.

These sensitivity analyses will be described in the SAP.

9.2.2.5 Supplementary analyses

The same analysis will be performed on the PPS [supplementary estimand #2, Table 4].

9.2.2.6 Subgroup analyses

The aim of the subgroup analyses is to explore the consistency of the treatment effect across the following subgroups:

- Age (18–29 vs 30–55 years)
- Sex (male vs female)
- Race (Black, Caucasian, other)
- BMI (< 30 vs ≥ 30 kg/m^2)

Results of the subgroup analyses will be displayed in a forest plot displaying treatment effects per subgroup and their 95% CIs (obtained by conducting the primary analysis by subgroup) with vertical reference lines at no effect as well as at the overall treatment effect. P-values for treatment by subgroup interaction will be provided for exploratory purposes, based on the primary analysis model extended with treatment by time and by subgroup interaction.

9.2.3 Analysis of the secondary efficacy outcome(s)

Not applicable.

9.2.4 Analysis of exploratory efficacy outcomes

Only the analyses of select exploratory endpoints [Table 2] are described here. The analyses of endpoints associated other objectives will be described in the SAP.

9.2.4.1 Variable definitions

- Changes from baseline up to Weeks 11–12 in the number of BE episodes per week based on diary data, defined based on the 2-week intervals defined for the primary endpoint. The number of BE episodes per week is defined as the number of BE episodes in the applicable 14-day time interval divided by the total number of diary days, times 7.
- Absence of BE episodes during the last 4 weeks of the treatment period, defined as no BE episodes during study days 57–84. A minimum of 4 out of 7 diary entries are required for days 57–63, 64–70,71-77 and 78–84, otherwise the outcome will be set to 'No absence'.
- Change from baseline to Week 12 in EDE-Q7 global score, defined as the difference of EDE-Q7 global score at Week 12 and at Baseline. Variables for the EDE-Q7 subscales are change from Baseline to Week 12 in EDE-Q7 dietary restraint subscale score, change from Baseline to Week 12 in EDE-Q7 shape/weight overvaluation subscale score and change from Baseline to Week 12 in EDE-Q7 body dissatisfaction subscale scores.

- CGI-C score at Week 12. Missing assessments at Week 12 will be imputed using last on-treatment observation carried forward. Study participants with no on-treatment assessment will have a missing value. Additionally, improvement according to CGI-C is defined as CGI-C at Week 12 equal to "Much Improved" or "Very Much Improved". If CGI-C at Week 12 is missing, the study participant will be assumed to not have improved.
- PGI-C score at Week 12. Missing assessments at Week 12 will be imputed using last on-treatment observation carried forward. Study participants with no on-treatment assessment will have a missing value. Additionally, improvement according to PGI-C is defined as PGI-C at Week 12 equal to "Much Improved" or "Very Much Improved". If PGI-C at Week 12 is missing, study participant will be assumed to not have improved.
- Change from baseline to Week 12 in the CGI-S score, defined as the difference of CGI-S score at Week 12 and at Baseline. Missing assessments at Week 12 will be imputed using last on-treatment observation carried forward.
- Change from baseline to Week 12 in the PGI-S score, defined as the difference of PGI-S score at Week 12 and at Baseline. Missing assessments at Week 12 will be imputed using last on-treatment observation carried forward.

9.2.4.2 Analyses

Other efficacy endpoints will be tested at the two-sided 5% significance level. No further Type I error control is applied, so these analyses are to be considered descriptive.

Change from baseline to Weeks 11-12 of the number of BE episodes per week

Changes from baseline to post-baseline time points will be analyzed using the same mixed model for repeated measurements as for the primary efficacy endpoint, only with a covariate for the baseline number of BE episodes (rather than the number of BE days) per week. Measurements obtained after premature treatment discontinuation will be excluded from the analysis [supplementary estimand #1, Table 4].

Absence of BE episodes during the last 4 weeks of the treatment period

Absence of BE episodes will be analyzed using a logistic regression model with a factor for treatment group, sex and BMI category and a covariate for the baseline number of BE episodes per week. For study participants who discontinued treatment prematurely, the outcome will be set to 'No absence'.

Change from baseline to Week 12 in EDE-Q7 global score and 3 subscales

Changes from baseline in EDE-Q7 scores will be analyzed using a mixed model for repeated measurements as described for the primary endpoint, but with less time points.

CGI-C score at Week 12

CGI-C scores will be compared between treatment groups using the Kruskal Wallis test.

Improvement according to CGI-C at Week 12

This variable will be analyzed using a logistic regression model with a factor for treatment group. The relationship between improvement according to CGI-C at Week 12 and the primary efficacy outcome will be investigated.

PGI-C score at Week 12

This variable will be analyzed using same methods as for CGI-C score at Week 12.

Change from baseline to Week 12 in the CGI-S score

Changes from baseline to Week 12 in CGI-S score will be analyzed in an analysis of covariance (ANCOVA) model with a factor for treatment group and a covariate for baseline score.

Change from baseline to Week 12 in the PGI-S score

This variable will be analyzed using same methods as for change from baseline to Week 12 in the CGI-S score.

9.2.5 Analysis of safety outcomes

The SAF will be used to perform all safety analyses.

Unless otherwise stated, only treatment-emergent safety data will be considered in tables and figures. All safety data will be included in listings.

9.2.6 Adverse events

9.2.6.1.1. TEAEs and SAEs

TEAEs and SAEs, including AESIs, will be tabulated by study treatment, SOC, and preferred terms within each SOC: the number and percentage of study participants who experienced at least one (S)AE, at least one (S)AE within each SOC, and at least one (S)AE within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity and by relationship to study treatment.

9.2.6.1.2. AEs leading to premature discontinuation of study treatment

AEs leading to premature discontinuation of study treatment will be summarized in a similar manner as that described in Section 9.2.6.1.1.

9.2.7 Laboratory data

9.2.7.1.1. Changes from baseline in laboratory variables

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values as well as for changes from baseline for laboratory tests (hematology, blood chemistry, urinalysis).

Data will be displayed in SI units whenever possible and graphical approaches may be applied for certain variables.

9.2.7.1.2. Treatment-emergent marked laboratory abnormalities

Laboratory abnormalities will be summarized descriptively by study treatment as categorical variables.

9.2.8 Vital signs

Descriptive summary statistics by visit and study treatment will be provided for observed values and changes from baseline in pulse rate, respiratory rate, temperature, systolic and diastolic blood pressure, and body weight.

Notable blood pressure abnormalities will also be summarized descriptively.

9.2.9 Electrocardiography

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and changes from baseline in numeric 12-lead ECG values (HR, and the intervals PR, QRS, QT, QTcB, and QTcF).

Treatment-emergent marked abnormalities for 12-lead ECG variables will be summarized at all visits.

In addition, morphological ECG abnormalities that were not present before first study treatment intake (using data from the ECG provider) will be summarized.

9.2.10 Specific safety endpoints

Daytime sleepiness is defined daily as any score > 3 on the SSS after taking the morning dose. It will be collected on Days 1–14 and expressed as a number of days per week (as for the primary efficacy outcome). A minimum of 7 diary entries are required, otherwise the data will be considered missing. The mean number of days with daytime sleepiness per week will be summarized by treatment group.

The number (%) of study participants with *suicidal ideation and/or behavior* based on the C-SSRS© will be tabulated by visit and treatment group.

Withdrawal effects will be described summarizing changes from changes from Week 12/EOT to EOS in BWSQ and HAMD-17 by treatment group.

9.2.11 Analyses of other outcomes

A full description of all other analyses will be provided in the SAP.

9.3 Interim analyses

No interim analysis is planned for this study.

9.4 Sample size

The sample size is based on the primary efficacy endpoint, change from baseline to Week 12 in the number of BE days per week.

In 2 studies using lisdexamfetamine in study participants with BED [McElroy 2016] the difference between lisdexamfetamine and placebo for this endpoint was –1.35 (SD = 1.6) and –1.66 (SD = 1.6) days per week. The corresponding effect size was 0.83 (95% CI: 0.60–1.05) and 0.97 (95% CI: 0.72–1.21), respectively. In the USA, lisdexamfetamine is categorized as a Schedule II medication. For this reason, a smaller effect size by ACT-539313 may still be considered clinically important if it has a better safety profile than lisdexamfetamine.

In an earlier study comparing topiramate to placebo in study participants with BED [McElroy 2007] the difference in the means of the changes from Baseline to Week 16 between topiramate and placebo was –1.0 with a common SD of 2.0, providing an effect size of 0.5 (95% CI: 0.3–0.7).

In a recent study with dasotraline, the LSmean reduction from Baseline in number of BE days per week was significantly greater for dasotraline vs placebo at Week 12 (−3.74 vs −2.75), for an effect size = 0.74 [McElroy 2020].

Based on the above, it is assumed that a treatment group difference of 1 BE day per week (corresponding to an effect size of 0.5 to 0.7, depending on the SD) is clinically meaningful.

The sample size is based on the power to detect a reduction of at least 1 BE day per week at Week 12 (with an SD of 1.6, this corresponds to an effect size of 0.65), between ACT-539313 and placebo, at a significance level of 5% two sided. Table 5 shows the sample size needed to detect a difference between placebo and ACT-539313 for different effect sizes.

Table 5 Total sample size for 90% power

Effect size	0.5	0.6	0.7
Power			
90%	170	118	86
80%	126	88	66

For a two-sided $\alpha = 0.05$ and 1:1 randomization

The sample sizes reported in Table 5 are based on a t-test, but are also valid for a mixed model for repeated measures, retaining close to 90% (or 80%) power in the case of missing Week 11–12 data (up to 20%).

Table 6 shows the power to detect a difference between placebo and ACT-539313 for a sample size of 100–120 study participants.

Table 6 Power for sample sizes of 100 and 120

Effect size	0.5	0.6	0.7
Sample size			
100	71%	85%	94%
120	78%	91%	97%

For a two-sided $\alpha = 0.05$ and 1:1 randomization

Assuming a sample size of 120 study participants (60 participants per arm), the power achieved in any of the scenarios described above, will be at least equal to 78% ($\alpha = 0.05$, two-sided).

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Regulatory and ethical considerations

The sponsor personnel and the investigators will ensure that the study is conducted in full compliance with ICH GCP guidelines, the principles of the "Declaration of Helsinki", and with the laws and regulations of the country in which the study is conducted.

The investigator and/or sponsor/CRO will submit this protocol and any related document(s) provided to the study participant (such as the ICF) to an IEC/IRB and to the health authority (as applicable). Approval from both the IEC/IRB and the health authority must be obtained before starting the study and must be documented in a dated letter to the

investigator and/or sponsor/CRO, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator/delegate and/or sponsor/CRO to the IEC/IRB and to the health authority in accordance with local procedures and regulations.

10.2 Informed consent process

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study and/or his/her legally designated representative. The investigator/delegate must explain to study participants that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention must be paid to the information needs of specific study participant populations and of individual study participants, as well as to the methods used to deliver the information. Adequate time must be given for the study participant and/or his/her legally designated representative to consider his or her decision to participate in the study and it must be verified that the study participant has understood the information (e.g., by asking the study participant to explain what is going to happen).

If a revised version of the ICF is approved by health authorities (if applicable) and IRBs/IECs:

- Newly recruited study participants and/or their legally designated representative must provide consent using the most current version of the ICF(s).
- Study participants who are already participating in the study (e.g., already recruited) and/or their legally designated representative must be re-consented using the most current version of the ICF(s) if necessary (e.g., additional study procedure, new safety information) and/or requested (e.g., as per IRB/IEC requirements).

A copy of the signed and dated ICF is given to the study participant and/or his/her legally designated representative; the original is filed in the site documentation. The informed consent process must be fully documented in the study participant's medical records. This must include at a minimum the study reference, the study participant number, the date and, if applicable, time when the study participant was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the study participant, and any additional person present during the consent process (e.g., study participant's family member[s]), and the information that a copy of the signed ICF was given to the study participant / his/her legally designated representative.

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the study participant and/or his/her legally designated representative will be listed on the Delegation of Authority form. A study physician must always be involved in the consent process.

If the site intends to recruit study participants who are considered to be vulnerable (e.g., study participant cannot read or write, does not speak or understand the ICF language), additional measures must be implemented to ensure the study participant's rights are respected and the consent obtained is legally valid. The sponsor, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before study participants are recruited.

10.3 Data protection and privacy

Study participant data confidentiality and privacy are strictly held in trust by the investigators, their staff and the sponsor or delegate.

The investigator/delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the sponsor and any vendors or CROs, study participants must be identified only by number and never by their name or initials, date of birth, hospital numbers, or any other personal identifier. The investigator/delegate must keep a study participant identification code list at the site. Documents identifying the study participants (e.g., signed ICFs) must not be sent to the sponsor or any vendors or CROs, and must be kept in strict confidence by the investigator/delegate.

In the BE Diary, there will be no possibility to enter any personal identifier and the study participant will only be identified by the study site and study participant number.

The study participants must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law.

The study participants must be informed that their medical records may be inspected by the sponsor or sponsor's delegate, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4 Indemnification, compensation and refund of expenses to study participants and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The indemnification of the study participant in the event of study-related injuries will comply with applicable regulations.

Study participants will be reimbursed for study-related expenses (e.g., travel costs, meals, hotel), and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local regulations.

10.5 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. Several attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or a certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into two different categories of documents: ISF and study participants' source documents.

These records must be kept by the investigator / trial site for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), ICH GCP and national and/or international regulations, whichever would be the longest period. If the investigator/ trial site cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator/site and the sponsor to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from the sponsor. If the site needs to transfer the study records to another location and/or if the site facility can no longer store the study records, the investigator/site must immediately inform the sponsor.

10.5.1 Investigator Site File

Each site will maintain an ISF. It will contain all the essential documents that are required to be up-to-date and filed at the site as per ICH GCP section 8.

The ISF must be stored in a secure and access-restricted area during and after the study.

10.5.2 Source documents

All source documents should be completed in a neat and legible manner to ensure accurate interpretation and traceability of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

If the site is using electronic/computerized system(s) to store study participant medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11) and if the CRA has been provided personal access to study participant's medical

records in order to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using electronic/computerized system to store study participant medical records but it could not be confirmed that the system(s) is/are validated (as per 21 CFR Part 11) or if the CRA could not be provided access to the system(s), the site is requested to print the complete set of source data needed for verification by the CRA. The printouts must be numbered, stapled together with a coversheet, signed, and dated by the investigator/delegate to confirm that these certified copies are exact copies containing the same information as the original source data. The printouts will be considered as the official clinical study records and must be filed adequately. Once printed and certified, the document must not be edited/changed (e.g., manual notes added, clinical value changed) in order not to impact the validity of the certification. In case the data needed to be changed (e.g., correction of a mistake) the change(s) must be done in the electronic/computerized system and a new copy must be printed and certified.

Entries recorded by the study participant in the BE Diary and SSS are considered source data.

10.6 Data handling

10.6.1 Data collection, data transfer procedure, and data access

The investigator/delegate is responsible for ensuring the accuracy, completeness, and timely reporting of study participant's data.

Electronic data capture will be used to collect eCRF data. The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification — an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (as per US 21 CFR Part 11).

Study participant recruitment and enrollment data will be completed for all study participants (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each study participant recruited, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those study participants who fail to complete the study.

Entries recorded by the study participant on the touchscreen device and on paper as well as the physician-reported global assessment on a touchscreen device at site and on paper are considered source data. Site personnel will review and ensure completeness and readability of the study participants' entries. If inconsistent data is detected by the site

personnel or indicated by the study participant, a data correction form will be completed by the site personnel to request any data changes and sent to the CRO provider that will process the changes as per CRO data management procedures.

10.6.2 Database management and quality control

The investigator/delegate will have "write" access to the site eCRF data until the end of the study. The investigators will be informed in a timely manner of "write" access removals. The eCRF must be completed in a timely manner as per eCRF completion guidelines.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by the sponsor personnel or delegate on an ongoing basis to look for unexpected patterns in data and for study monitoring. Should discrepant data be detected, a query specifying the matter and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator/delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the case of health authority queries, it is also necessary to have access to the complete study records, provided that study participant data confidentiality is protected.

This process will continue until database lock.

Laboratory samples, ECGs, and touchscreen device data will be processed through a central vendor and the results of the enrolled study participants will be electronically sent to the sponsor at pre-specified intervals with a final transfer prior to database lock. During the course of the study, the site staff and sponsor representatives can access the data in view-only mode on the central server of the respective vendor [see also Section 10.6.1]. Respective vendors will generate their own queries/programmed checks based on their respective data management plans.

AEs and medical history are coded with MedDRA. Medications are coded with the WHO Global Drug Dictionary.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the appropriate sponsor/CRO Quality System documents. The investigator/delegate will have read-only access to the site eCRF study participant data, until receipt of an electronic copy of the site eCRFs (including the audit trail).

10.7 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

The investigator must conduct the study in compliance with the IEC/IRB-approved and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the study participant.

Protocol deviations must be reported to the IEC/IRB and regulatory authorities according to local requirements.

Reporting of protocol deviations related to the COVID-19 pandemic

Despite the provisions made to allow flexibility and adaptations to the per protocol schedule of assessments, protocol deviations due to COVID-19 are expected to occur during the pandemic and fall under the ICH GCP 4.5.4 "The investigator may implement a deviation from, or change of, the protocol to eliminate an immediate hazard(s) to trial subjects".

Any protocol deviation occurring due to COVID-19 must be documented according to ICH GCP 4.5.3 and be clearly recorded as related to COVID-19. All protocol deviations will be reported to the sponsor, IEC/IRB and regulatory authorities according to local requirements.

10.8 Clinical monitoring

Prior to study start at a site, all required approvals must be obtained. A site initiation visit will be performed after the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all key site personnel involved in the study are present/available during the site initiation visit and will dedicate enough time to it.

The site initiation visit must be completed before the site can start recruiting study participants. Following the site initiation visit, a copy of the completed initiation visit report and follow-up letter will be provided to the PI and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being

entered in the eCRFs and other protocol-related documents. Monitoring activities will be performed according to the study-specific monitoring guidelines. The methodology and the frequency of the monitoring visits will be mainly based on study participant recruitment rate and critical data-collection times.

The PI/delegate must ensure that the eCRF is completed as per the eCRF completion guidelines and that all requested study participant files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The PI agrees to cooperate with the CRA to ensure that any issues detected in the course of these monitoring visits are resolved.

A close-out visit will be performed for any initiated site when there are no more active study participants and all follow-up issues have been resolved. If a site does not screen any study participants, the close-out visit may be performed prior to study closure at the discretion of the sponsor.

Monitoring during Covid-19 pandemic:

If on-site monitoring cannot be performed by the CRA as described above, and if deemed acceptable under local law with the IEC/IRB, the CRA will conduct remote monitoring and remote source data verification, provided that the study participant's confidentiality is maintained throughout the process and all local approvals to do so are in place. If remote monitoring or remote SDV are not allowed, alternatives as applicable, according to local regulations, may be agreed with the PI to ensure data integrity.

10.9 Study safety oversight

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific examinations, as required) are monitored and reviewed on a continuous basis by the sponsor.

The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of monitoring safety. Such additional data may be shared with external experts.

10.10 Premature termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is suspended or prematurely terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or prematurely terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all recruited study participants and ensure their appropriate treatment and follow-up, as described in Section 6.3. The sponsor may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the study participants' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from the sponsor, the investigator must promptly inform the sponsor personnel and the IEC/IRB and provide both with a detailed written explanation of the termination or suspension.

10.11 Audit

The sponsor representatives may audit the investigator site during the study or after its completion. The purpose of this visit will be to determine the investigator's adherence to ICH GCP, the protocol, and applicable regulations. Adherence to the sponsor requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., study participant records) and facilities.

10.12 Inspections

Health authorities and/or IEC/IRB may also conduct an inspection of this study at the site (during the study or after its completion).

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform the sponsor (usually via the CRA and copying the following mailbox: gcp@idorsia.com) that such a request has been made.

The investigator and site personnel must cooperate with the sponsor to handle the inspection related to sponsor studies. The investigator and site personnel must also cooperate with inspector(s) to ensure proper performance of the inspection and allow access to all study documentation (e.g., study participant records) and study facilities.

10.13 Reporting of study results and publication

The sponsor will post the key elements of this protocol and the summary of results within the required timelines on publicly accessible databases (e.g., clinicaltrials.gov), as required by law and regulation.

Study results will be documented in a CSR that will be signed by the sponsor's representatives and the coordinating investigator.

In accordance with the Good Publication Practices and ethical practice as outlined in internationally recognized guidance documents (e.g., European Medical Writers Association, American Medical Writers Association, International Society for Medical Publication Professionals), the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The coordinating investigator will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with the sponsor personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Medical Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

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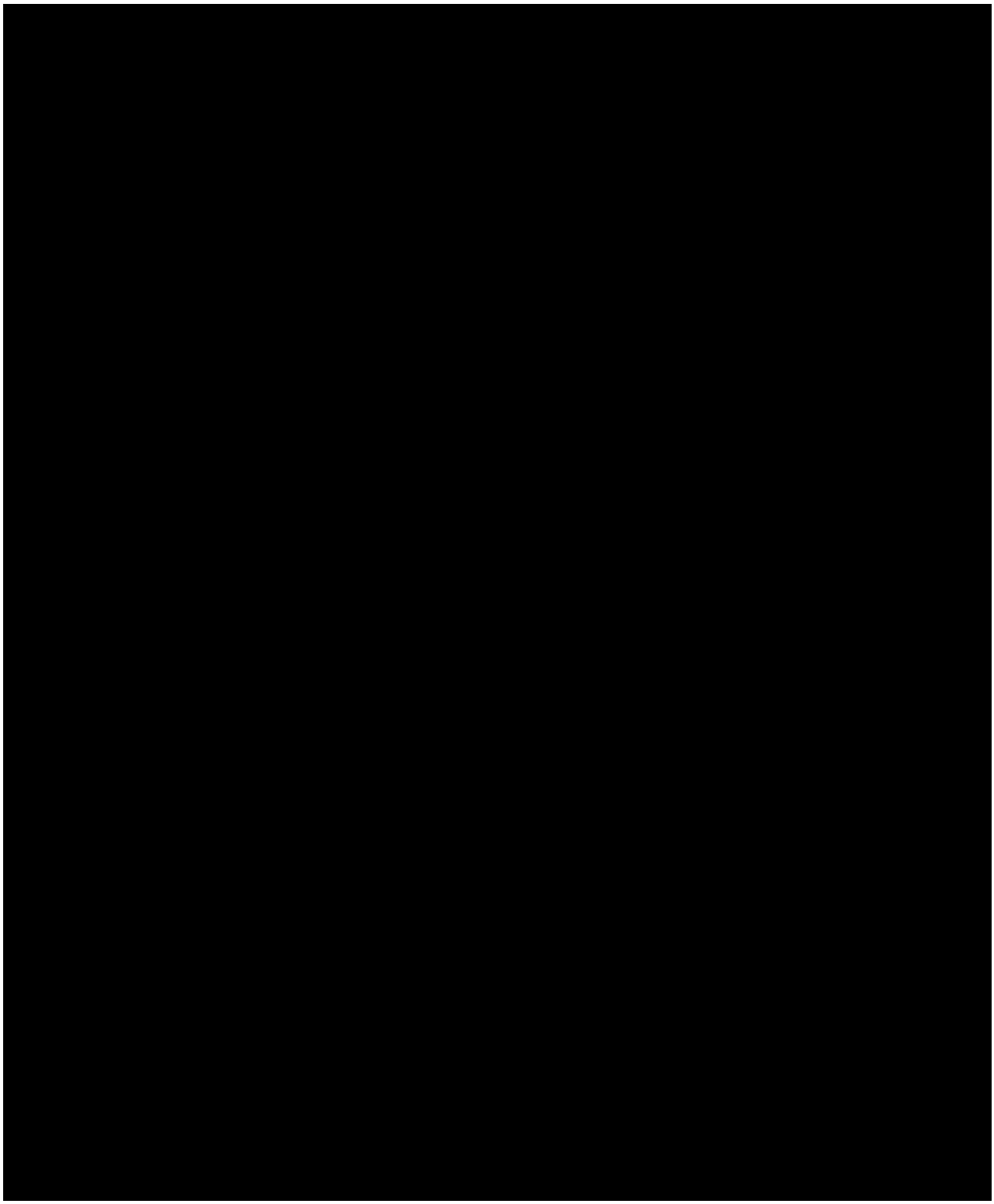
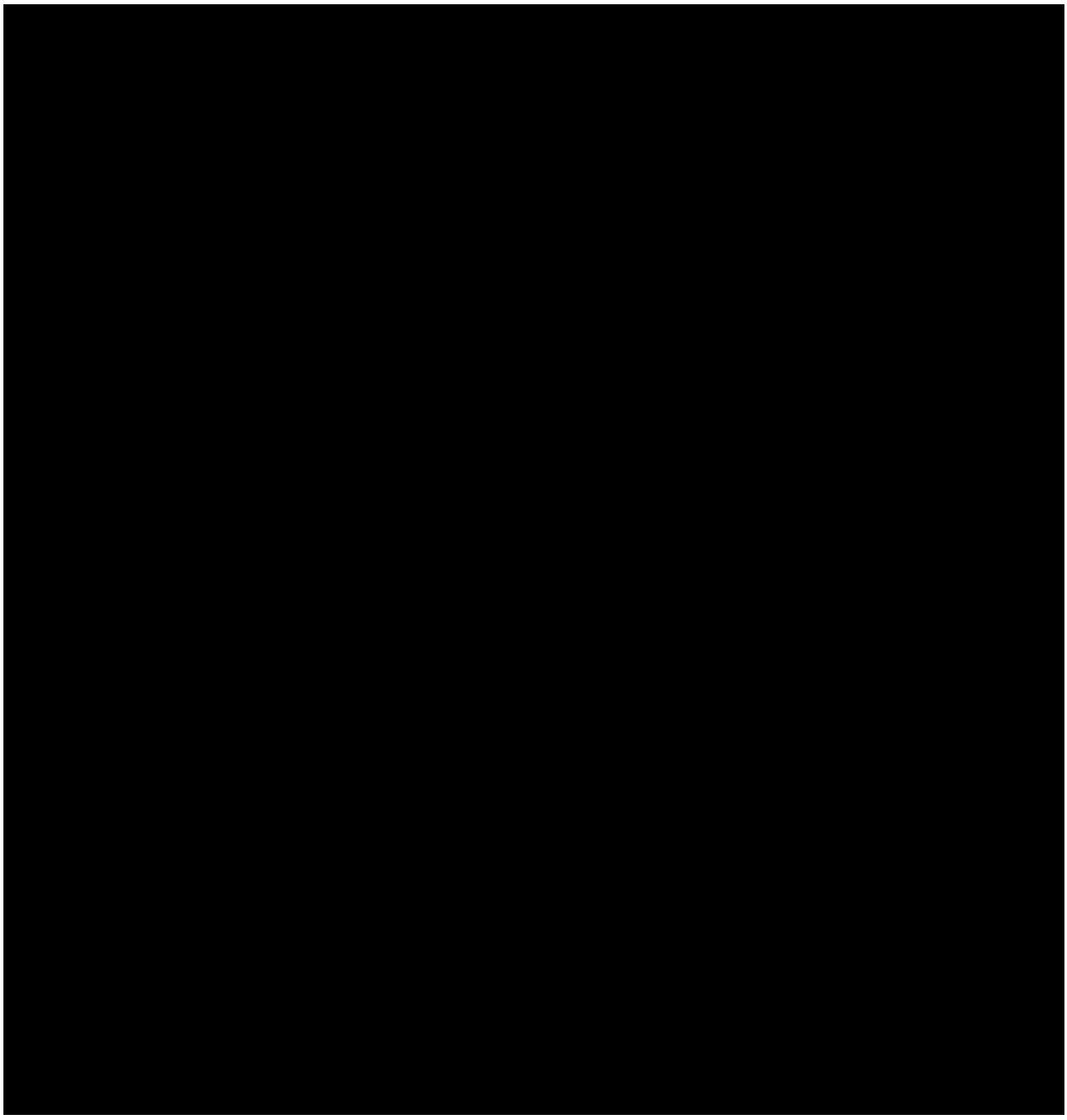
12 APPENDICES





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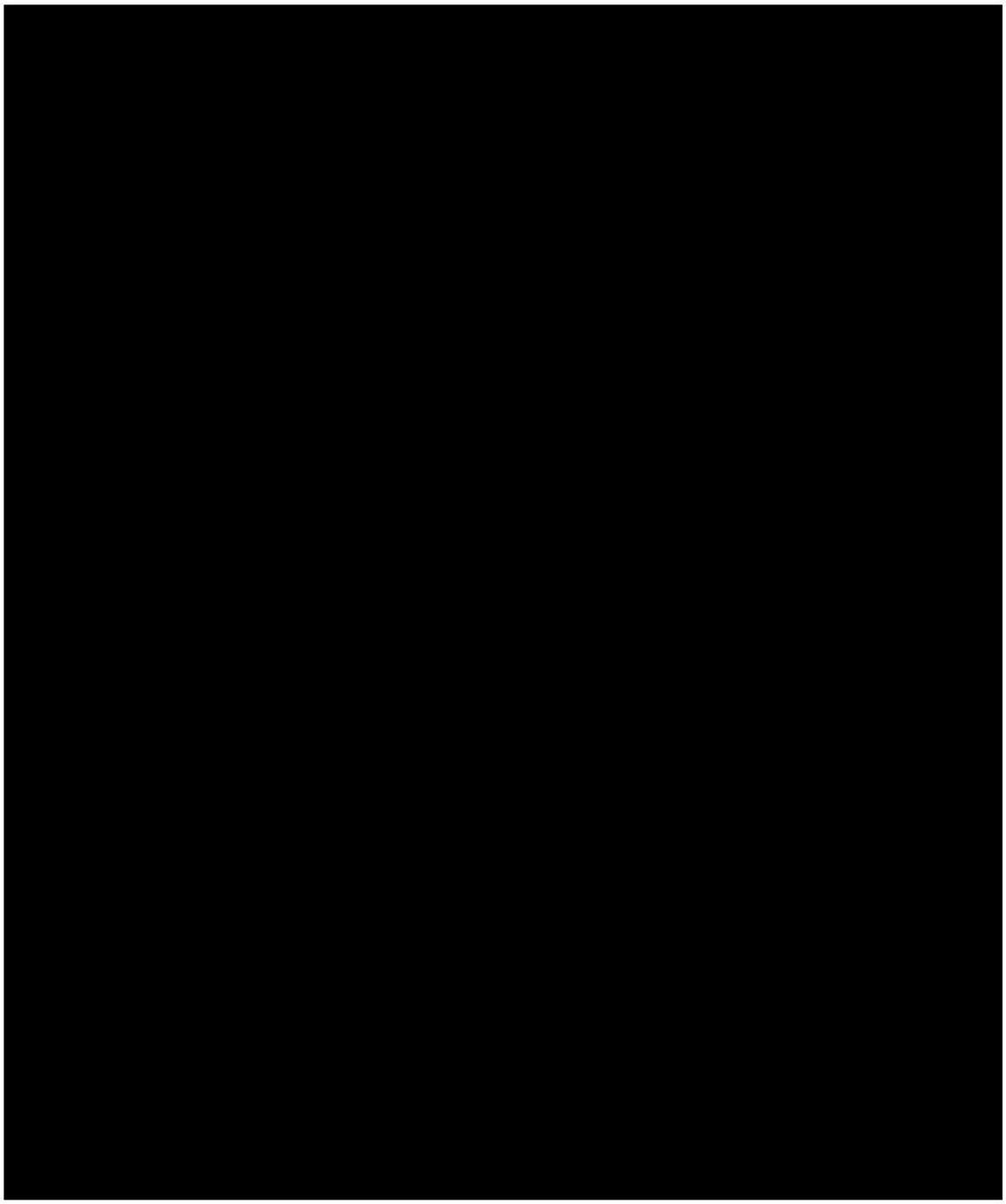

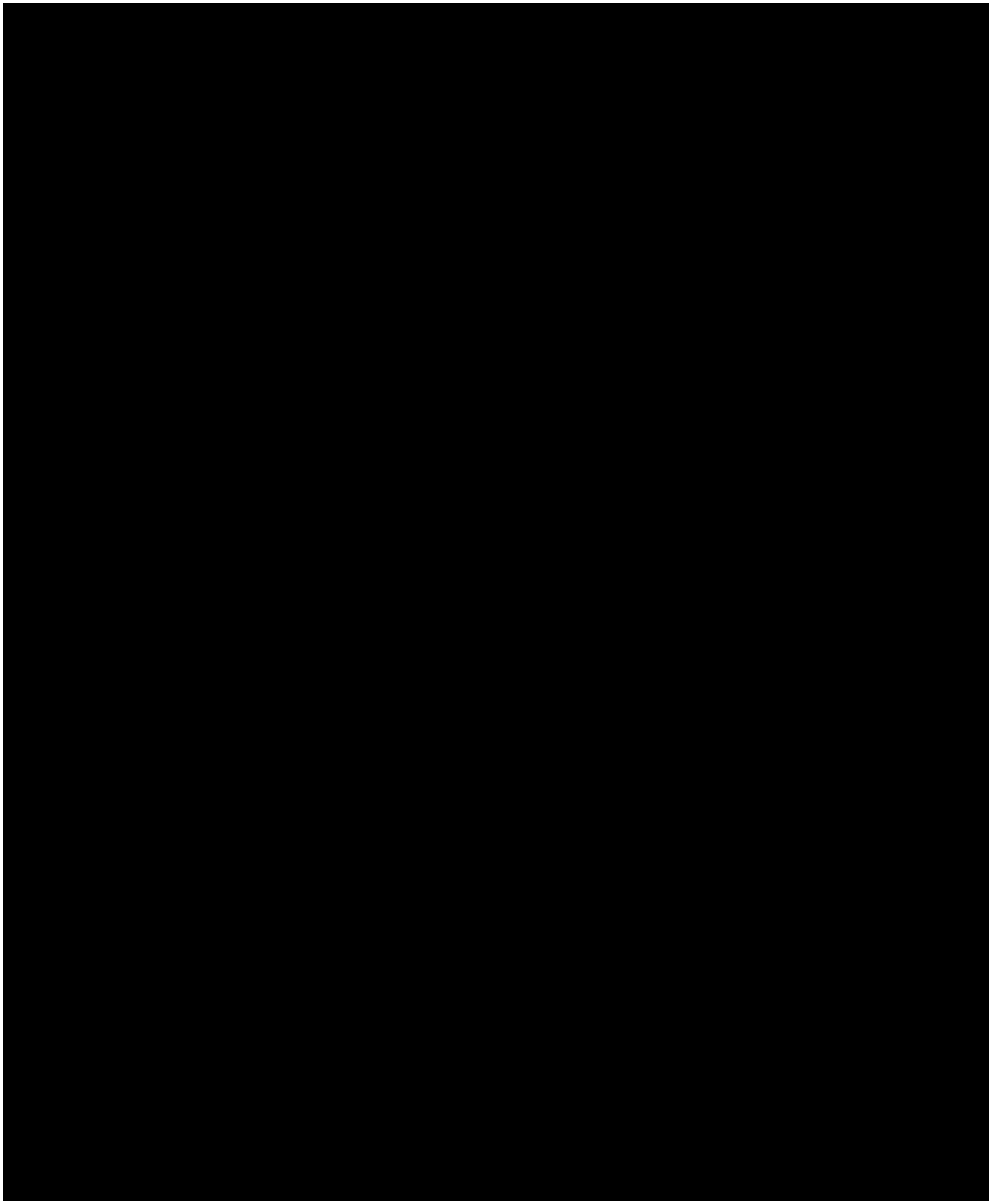

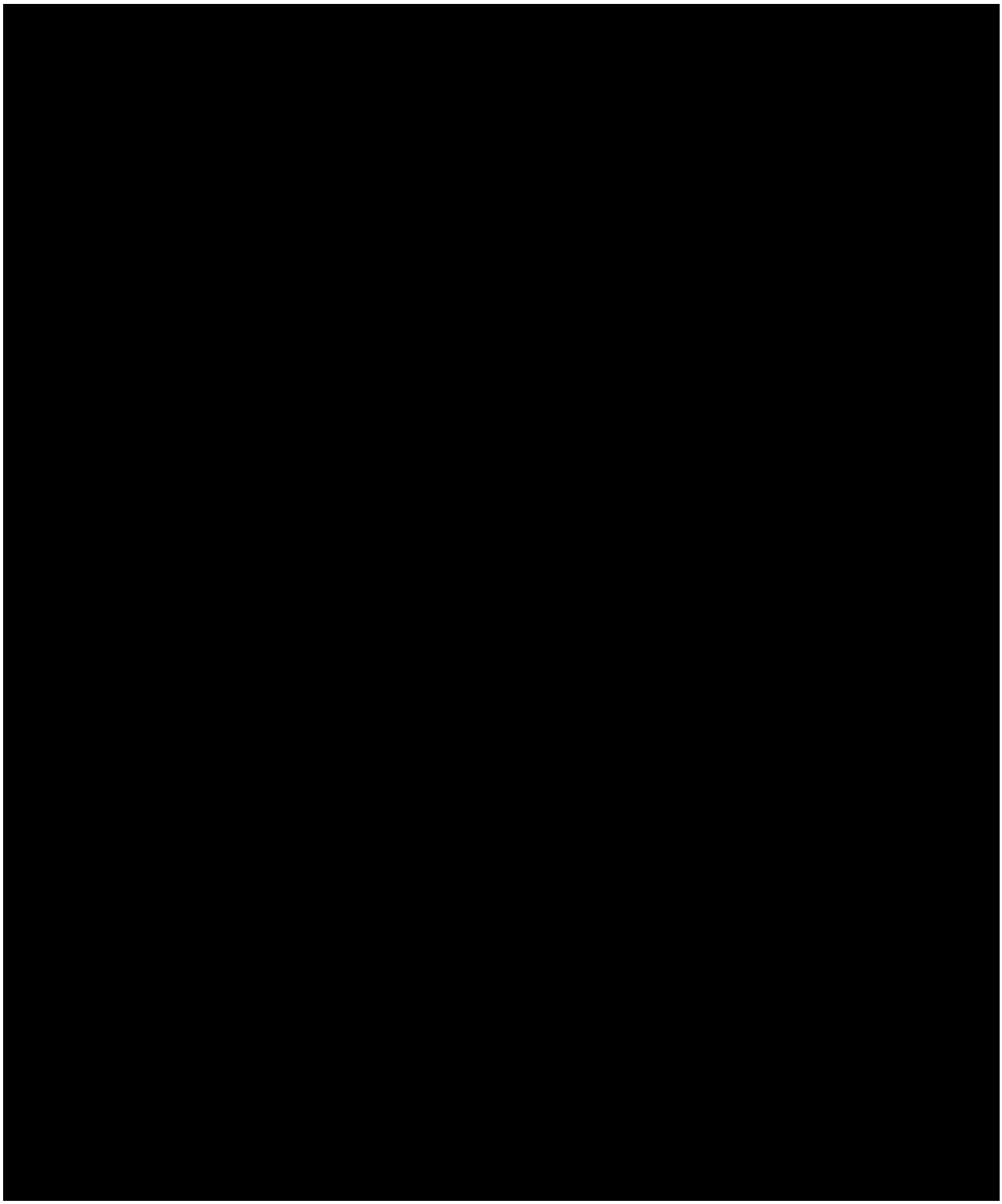

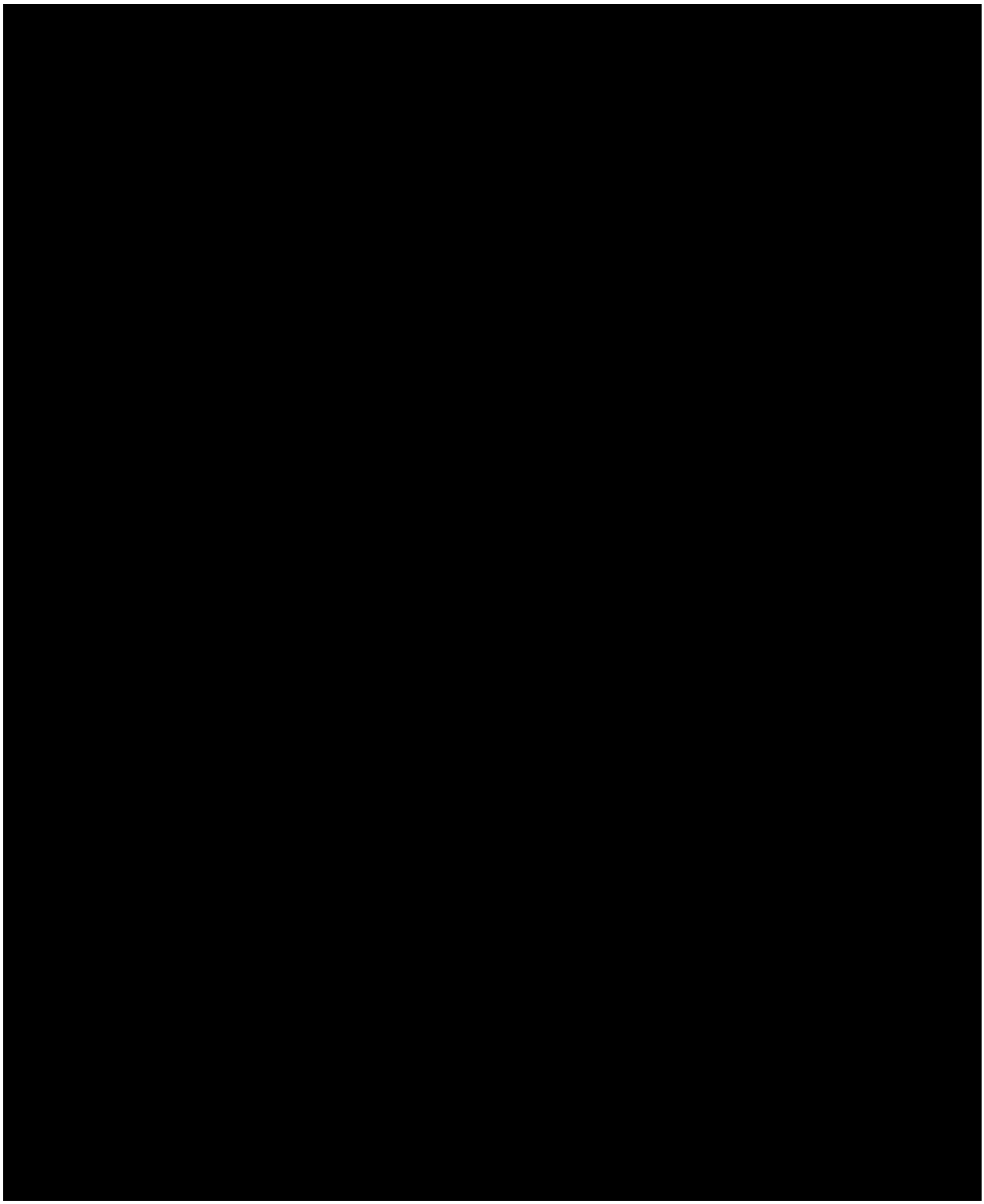

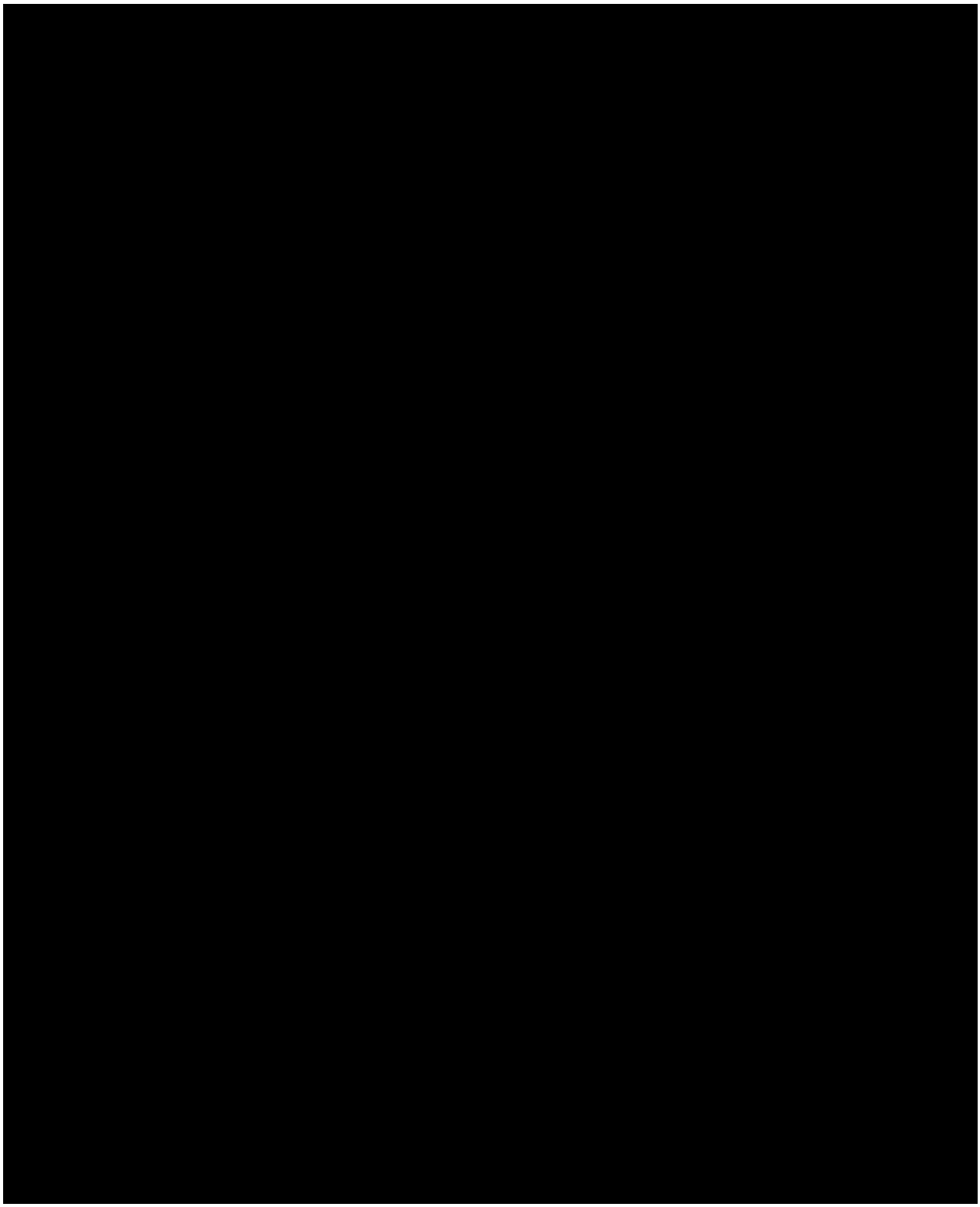

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